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Editor

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Volume 103 of our series contains three substantial chapters. M.M. Krayushkin and M.A. Kalik (affiliated with Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow) summarize synthetic work directed to photochromic dihetarylethenes. Work has been especially concentrated on dithienylethenes that have considerable potential derived from photochemically induced isomerizations between the *cis*- and *trans*-forms and cyclized derivatives.

G. Fischer (Leipzig, Germany) has provided the first definitive review of pyrido[1,2-*a*]azepines and their hydro derivatives. These compounds of growing interest and importance have a large literature of their own, now conveniently summarized for the first time.

Y.M. Litvinov and A.M. Shestopalov (also of the Zelinsky Institute of Organic Chemistry) have summarized the synthesis, structure, reactivity, and practical significance of 2-amino-4*H*-pyrans. Although the first representatives were reported only in the middle of the 20th century, recent interest in this class has increased because of the discovery of interesting biological activity. Until now there has been no comprehensive review.

Alan Katritzky

Syntheses of Photochromic Dihetarylethenes

Mikhail M. Krayushkin and **Marina A. Kalik**

1. INTRODUCTION

Photochromic transformations of difuryl- and dithienylethenes (DTEs) **I** under UV light were described for the first time in the 1960s by Kellogg (67JOC3093) (Scheme 1), who studied the photocyclization of stilbene-like aromatic and heteroaromatic compounds.

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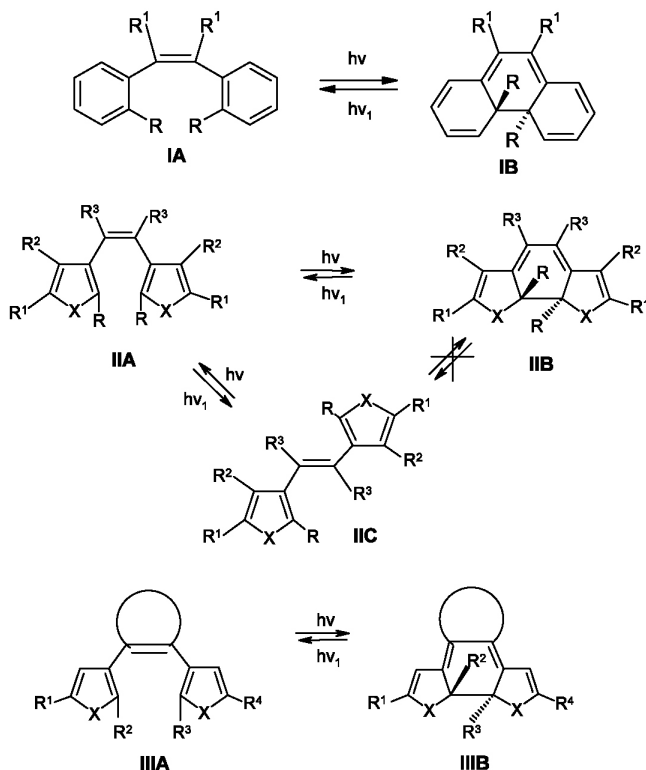
Scheme 1

Twenty years later, Japanese Professor M. Irie showed there is a fundamental difference in the behavior of stilbenes **I** and their heteroanalogs **II** (X = O or S). Under UV irradiation, stilbenes **IA** undergo cyclization to phenanthrenes **IB**, which are isomerized spontaneously to the starting stilbenes even in the dark. Irie found that, unlike phenanthrenes for the heteroanalogs, the cyclic **IB** are much more stable even at high temperatures (88JOC803). The theoretical explanation of this phenomenon was suggested in 89MI1 and 10PJA472.

Since the photocyclization of stilbenes and dihetarylethenes (DHEs) is accompanied by *cis–trans* isomerization, and the *trans* isomers **IIC** do not give a cyclized form, the next logical step was to synthesize products **II** with a fixed *cis* conformation, in which the thienyl or benzothienyl moieties are linked to the double bonds of perfluorocyclopentene, maleic anhydride, and maleimide. Later on, it appeared that photochromes containing such "bridges" possess not only thermal irreversibility but also high fatigue resistance, amounting in some cases, to 10,000 cycles.

These properties combined with other useful physicochemical characteristics offer ample opportunities for the use of dihetarylethenes in nonlinear optics, optical memory devices, as photoswitches, linkers, display elements, etc. Some dihetarylethenes, such as bis(indolyl)furan-2,5-diones, which were covered by patents as typical photochromes (93JAP05039289, 94JAP06161024), have a broad spectrum of biological activities (98PIA9811105, 99PIAWO9947518, 99USP5891901). Due to a unique combination of these properties, dihetarylethenes have attracted great interest in the last decade. They were considered in a number of reviews (98BCJ985, 00CR1685, 01KGS19, 02AFM167, 03MI1, 04BCJ195, 04CRC23, 04CSR85, 04MI1, 05CSR327, 05EJO1233, 05PC826, 06PC698, 07CC781, 07CJOC175, 07COC1259, 08JPP(A)10, 08JPP(C)61, 09JPP(C)111, 10JPP(C)1, 10PJA472). Most of these reviews were focused on the physicochemical and optical data, and only a few included data on the synthesis of these photochromes (01KGS19, 04CSR85, 07CJOC175, 07COC1259). It is of interest to summarize the methods for the synthesis of photochromic dihetarylethenes (primarily of dithienyl- and dibenzothienylethenes). With a few exceptions, the photochromic properties and the structures of the products are not considered in the present review and will be discussed elsewhere. The data on polymers based on dihetarylethenes, as well as the data on metal complexes containing photochromic ligands, are also beyond the scope of the present review because most of these publications were concerned with peripheral transformations not associated with the design or characteristic transformations of dihetarylethene systems. In essence, we systematize methods for the synthesis of compounds **III**, in which both heterocycles are in vicinal positions at the double bond of cyclopentene, perfluorocyclopentene, and various heterocyclic moieties.

The terms "diarylethenes," "dithienylethenes," and "dihetarylethenes," as applied to the structures of photochromic products **II**, of course, do not strictly meet the nomenclature requirements. However, these terms have gained wide acceptance in the special literature. The classification of compounds containing heterocycles as bridges is also rather arbitrary.

2. SYNTHESIS OF PERFLUOROCYCLOPENTENE-BRIDGED DIHETARYLETHENES

Photochromic dithienyl- and dibenzothienylethenes, particularly those containing the central 1,2-perfluorocyclopentene fragment, belong to the major group of compounds, which have attracted the attention of researchers in the field of information storage (optical memory) and optical switches because their starting (A) and cyclic (B) forms are, in most cases,

stable in the absence of photoirradiation up to their decomposition temperatures (03CPL206), as well as due to their high fatigue resistance.

2.1 Reactions of lithium derivatives of thiophene with octafluorocyclopentene

The most widely used method for the preparation of perfluorocyclopentene-containing DTEs is based on the reactions of lithium derivatives of thiophene with octafluorocyclopentene (98KGS927, 99IZV979, 99JP183). This method is used for the assembly of photochromic products from components indifferent to butyllithium or for the formation of the core of the molecules for their subsequent functionalization. This approach is suitable for the synthesis of both symmetrical and unsymmetrical photochromes.

2.1.1 Symmetrical DTEs

Here typical syntheses of symmetrical products are considered. In Scheme 2, the treatment of bromide **1** with butyllithium under standard conditions in the presence of perfluorocyclopentene affords photochrome **2** (31%) (99IZV979). Derivatives **3** and **4** were synthesized in a similar way (98KGS927).

Interestingly, **4** containing ethylthio groups at positions 2 and 2′ of the thiophene rings, which was prepared from isomeric bromide **3**, does not exhibit photochromic properties, as opposed to typical photochrome **2**. This fact remains unclear because even **5** (Scheme 3) containing the electron withdrawing and bulky benzothiazole fragments is a typical photochrome (01RCB110), like structurally similar dithienyl-(01CL618) and dithiazolylperfluorocyclopentenes containing the methoxy
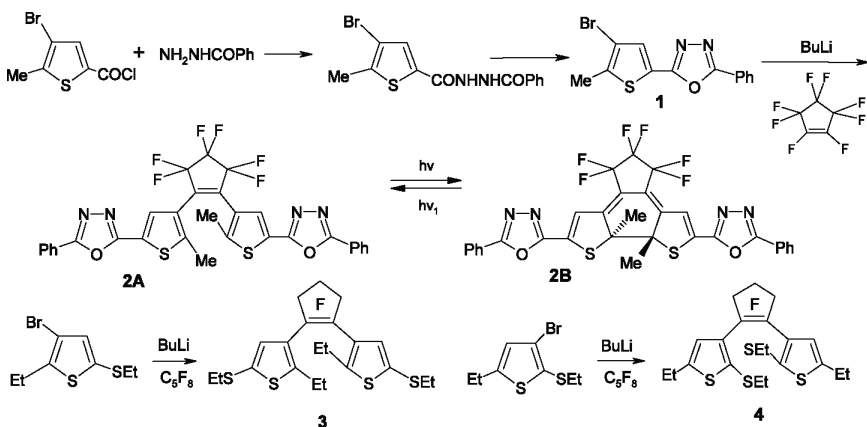
Scheme 2
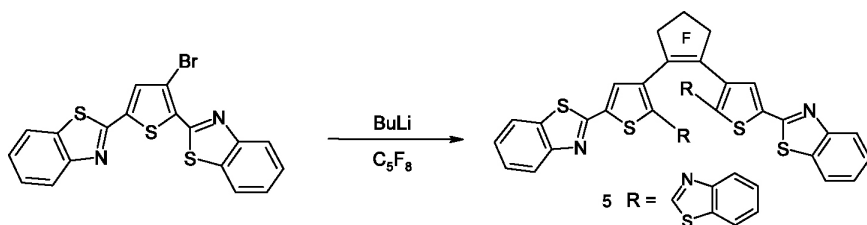
Scheme 3

(02EJOC3796) or ethoxy (07JMC4414, 09AM309) groups in the reaction center.

An alternative method for dithienylperfluorocyclopentenes is based on the functionalization of the presynthesized dithienylethenes having, as a rule, very simple structures. Scheme 4 shows a part of the synthetic route (the assembly of unique photochrome **7** performed by Lehn and coworkers) by a Suzuki reaction starting from available boronic acids **6** (96CEJ1399). This reaction is widely used for the modification of the dihetarylethene moiety by aromatic substituents. This scheme also gives the "reverse" example of the synthesis of **9**, where the boronic acid fragment is present in **8** (07JPP(A)202).

A successive increase in the chain length in dithienylethene **6** by a Suzuki reaction leads to the formation of polythienyl photochromes **10** (Scheme 5).
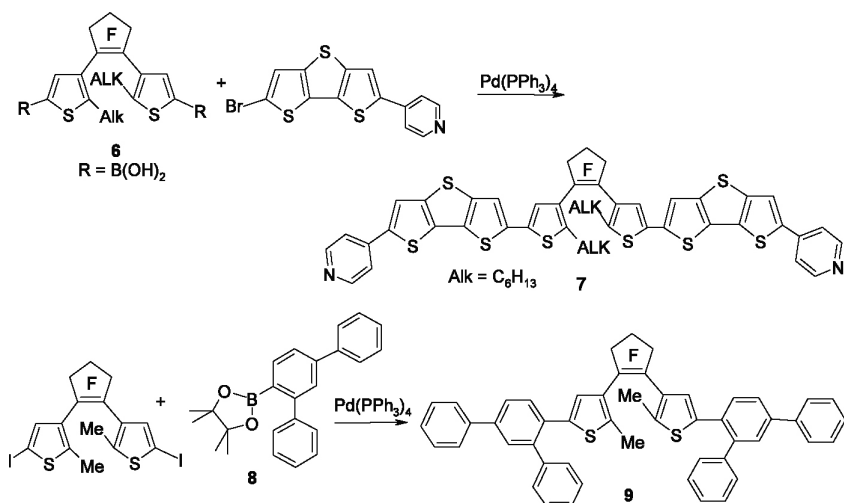
Scheme 4
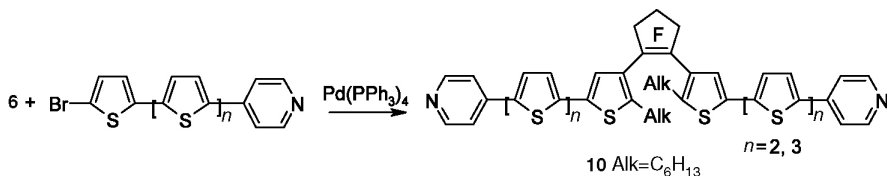
Scheme 5

Similar oligomeric products were described in 97T214. The synthesis and properties of conducting polymers containing a structurally similar photochromic dihetarylethene fragment in the main or side chain were reported (99CL905, 05CL1580). Examples of the subsequent functionalization of photochrome **3** by the introduction of substituents at positions 4 and 4′ of the thiophene rings (Scheme 6) were given in 00IZV1778.

Products **11–15** are convenient starting compounds for the synthesis of photochromes with fused heterocycles, as well as of polymers. However, the reactivity of the bromine atoms in **11** is limited by steric factors. Thus, lithium (and then carboxy) derivatives of **13** are formed in high yields, whereas attempts to introduce formyl groups at positions 4 and 4′ with DMF failed.

Chinese researchers reported a synthetic route to photochrome **16** (Scheme 7), in which the aldehyde functions are then transformed into cyclic acetals and thioacetals, methylol and dicyanoethylene groups (07T5437, 08T2576). Scheme 7 also gives (at the bottom) symmetrical photochrome **17** (where R are ferrocenyl substituents), which does not exhibit fluorescence in the initial state, but shows fluorescence in the cyclic form and which is also synthesized starting from dialdehyde **16** (08AFM302).
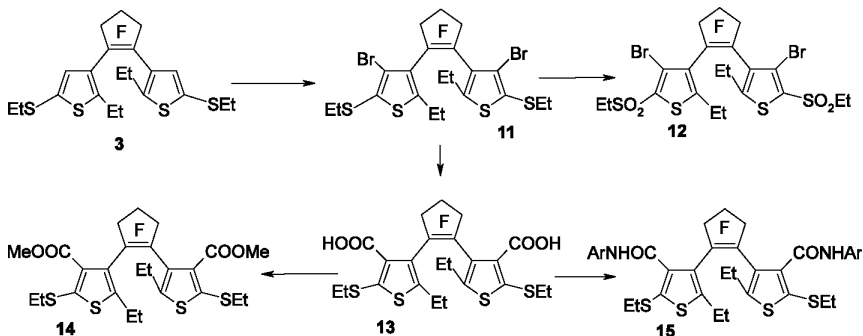
Scheme 6
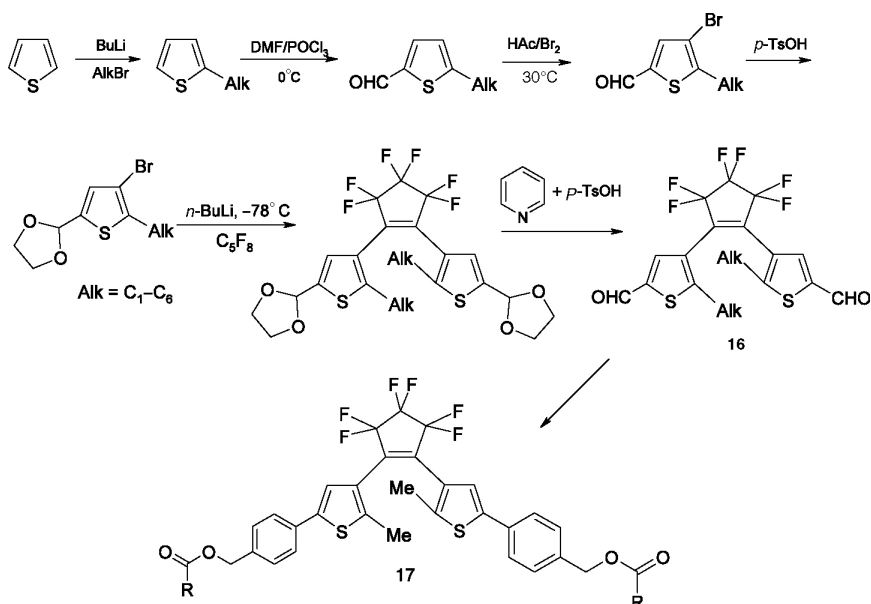
Scheme 7
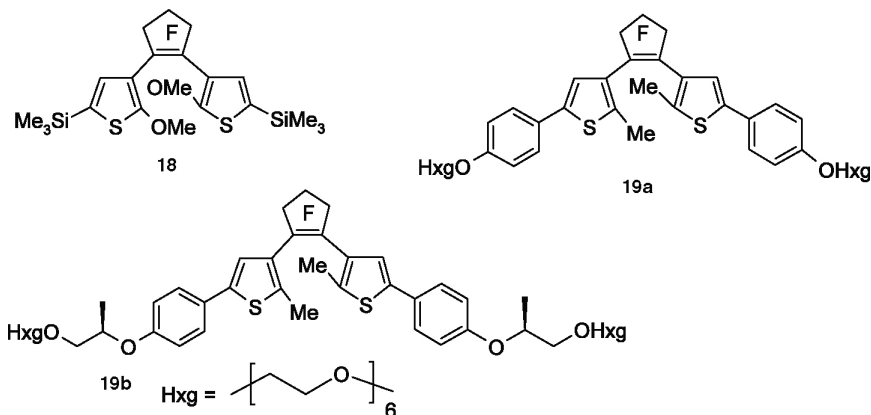
The numerous symmetrical photochromic products include relatively structurally simple trimethylsilyl derivatives **18** exhibiting the superhydrophobic effect (06AG(E)6470), water-soluble photochromes **19a** and **19b** containing the hexaethylene glycol fragment in the side chain and having self-assembly reactivity (06JOC7499, 09CAJ58), metal chelates **20** (M = Ag, Ru(II), or Os(II)) (04IC2779, 06ICA4281), dicoumarin derivatives **21** (05TL9009), and fluorescent product **23** (05JOC5545), which was prepared

by the Sonogashira reaction in the presence of Pd$_2$(dba)$_3$ starting from 4,4-difluoro-8-(4′-iodophenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene and acetylene **22** (01JOC3913).
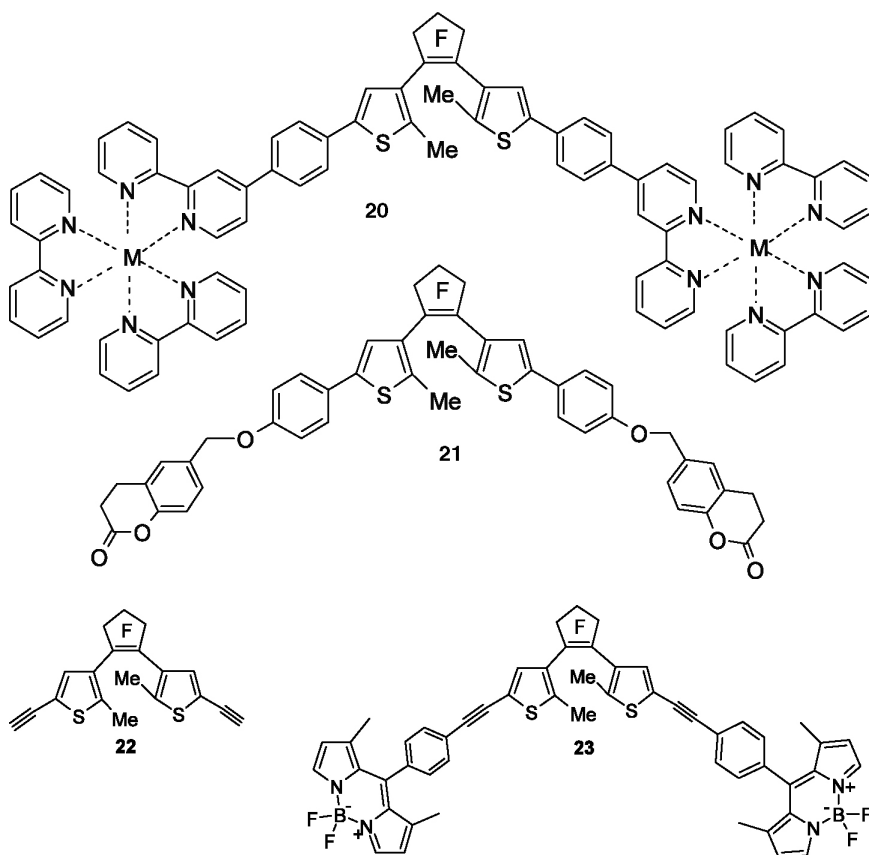
2.1.2 Unsymmetrical DTEs

All the above examples refer to thiophenes containing functional groups indifferent to the presence of butyllithium. In reactions with reagents in an equimolar ratio, it is highly probable that only one of the fluorine atoms at the double bond of cyclene will be replaced. For example, the target product **26** (Scheme 8) was prepared by either a one-pot reaction in the presence of a twofold excess of lithium derivative **24** with respect to perfluorocyclopentene or in two steps including the isolation of monofluoride **25** (99IZV1011).

Moreover, the monosubstitution products can be isolated and involved in subsequent transformations giving unsymmetrical photochromes (Scheme 9) (99EJO2359).
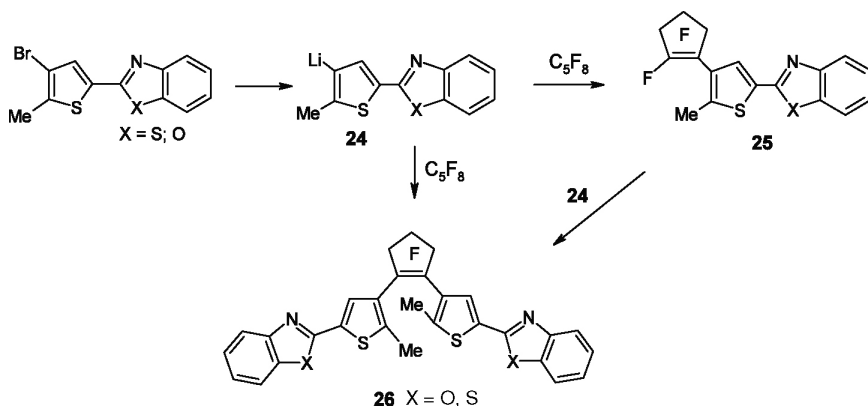
Scheme 8
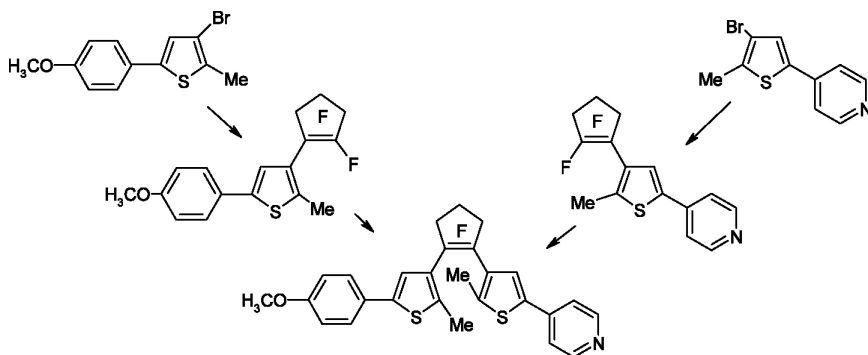
Scheme 9

Typical syntheses of unsymmetrical derivatives include **27** (98CL1123), **28** (08SA1065), and **29** (Scheme 10). The perfluorocyclopentene fragment in the latter compound is bound to different positions in the thiophene moieties (95CL969, 04CC1010).

Functionalized unsymmetrical 1,2-bis(3-thienyl)perfluorocyclopentenes **30–32**, in particular those containing one free α position in the thiophene ring, were also synthesized according to the above-described method. These compounds can be used for the preparation of various new photochromes (03MI2, 05KGS691). Unsymmetrical isomeric diarylethenes **33** containing the methoxy (09JPOC954) or cyano (10DP1) substituents in the *ortho*, *meta*, and *para* positions of the terminal benzene ring were synthesized by the Suzuki reaction of 3-bromo-2-methyl-5-thienyl-boronic acid with the corresponding isomeric bromobenzene derivatives (Scheme 11).
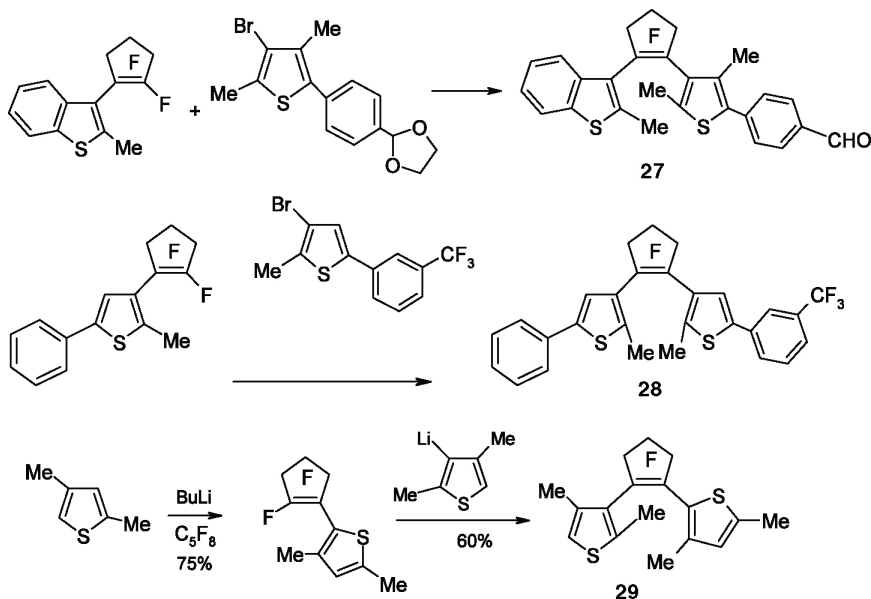
Scheme 10
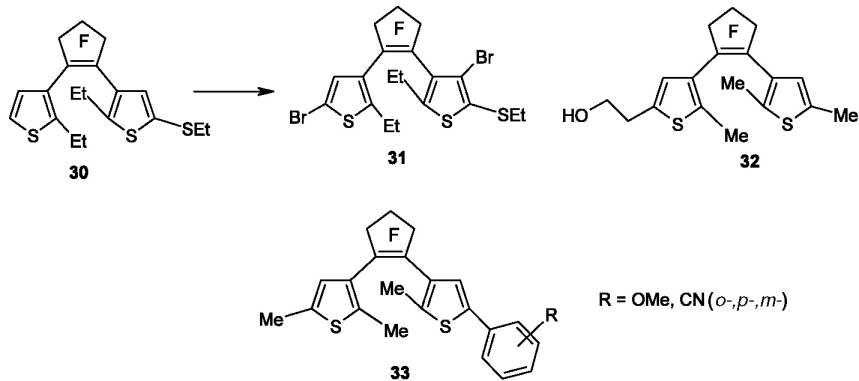
Scheme 11

A nontraditional type of photochromic dihetarylethenes bearing a six-membered aryl moiety was described (08T9464). Compounds **34** were prepared from 2-methyl-5-phenyl-3-thienylperfluorocyclopentene by a one-step coupling reaction with 2-bromoanisole, 2-bromotoluene, 2-bromobenzonitrile, and 2-bromobenzotrifluoride, respectively (Scheme 12).

Other unsymmetrical compounds include dipolar photochromic Zn(II) dipyridyl complexes **35** with nonlinear optical properties (08AG(E)577),
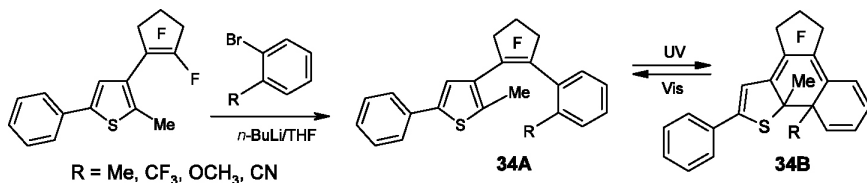
Scheme 12

charge-transfer complexes with a photochromic electron donor **36** and with 7,7,8,8,-tetracyano-2,3,5,6-tetrafluoro-*p*-quinodimethane as an electron acceptor (06CC2656), photochromic oligothiophenes **37** (CL1580), and long-chain dinitroxide radicals **38** (05P2484).
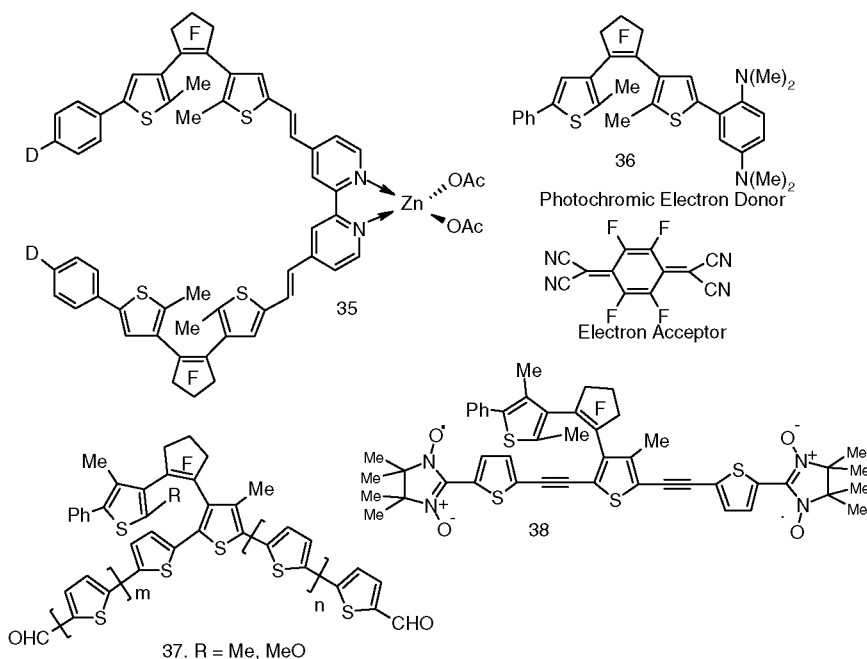
From numerous examples of the synthesis of symmetrical and unsymmetrical dithienylperfluorocyclopentenes here are given the scheme for the preparation of photochromic products containing the terminal thiol group **40** and **41** on the base of trimethylsilyl derivative **39** for the subsequent synthesis of gold and silver nanoparticles (04CL456, 06BCJ1413, 07CC1355) (Scheme 13).

The structures of unsymmetrical photochromic **42**, which is also intended for the use in the synthesis of metal nanoparticles enclosed by dihetarylethenes (07CC1355), and fluorescent **43**, which was prepared in 05JOC5545, are illustrated.
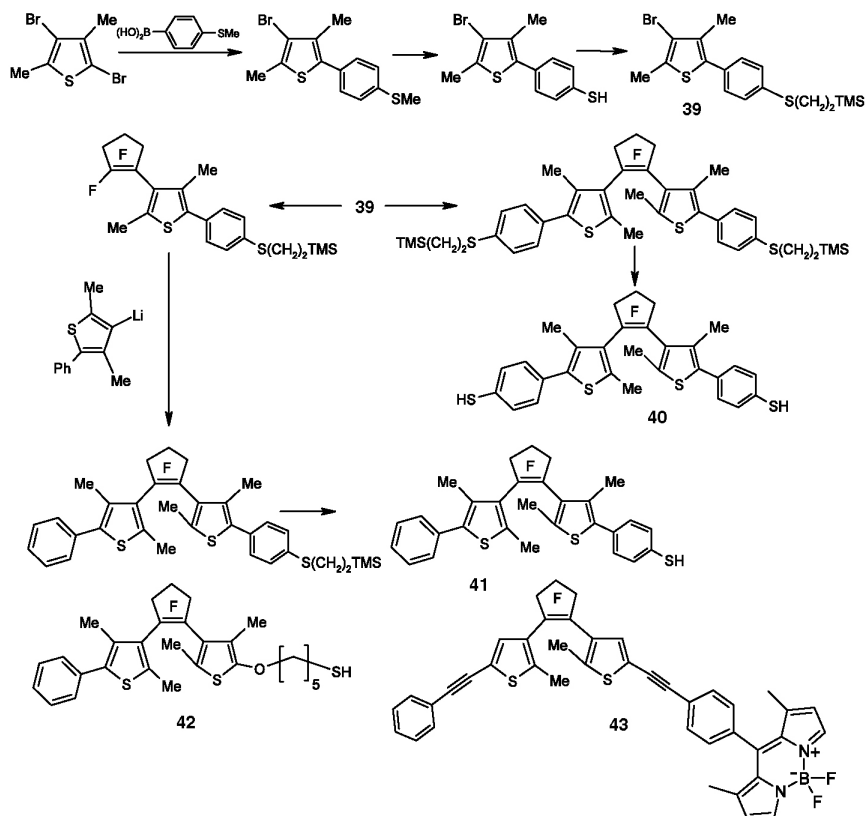
Scheme 13

2.1.3 DHEs based on fused thiophenes and other heterocycles

In addition to thiophenes, the above reactions of perfluorocyclopentene, as well as of fluorinated derivatives of cyclobutene and cyclohexene, can be carried out with fused thienyl derivatives and various heterocycles forming relatively stable anions.

2.1.31. Benzo-, thieno-, and dithienothiophenes

The family of photochromic products, in which the benzothiophene rings are bound to perfluorocyclenes (Scheme 14), was described for the first time in 92CC206. These compounds have attracted attention because they, as a rule, have a higher fatigue resistance compared to the corresponding thienyl derivatives (98BCJ985). The method for their synthesis is virtually identical to that described above for DTEs and is characterized by high regioselectivity.

A series of symmetrical and unsymmetrical derivatives containing electron-donating and electron-withdrawing substituents at position 6 of
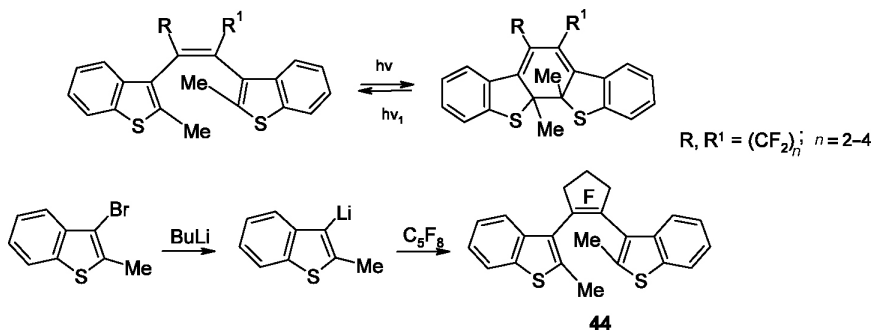
Scheme 14
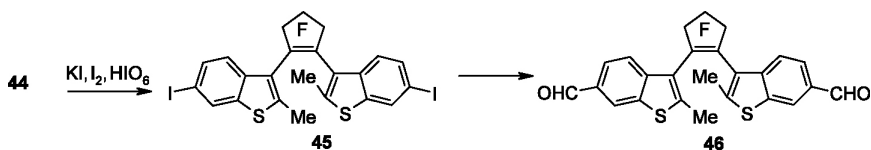
Scheme 15

the benzothiophene ring, for example, CHO, CH=CHC$_6$H$_5$ (02M8684), (NO$_2$, I) (06T6814), were synthesized based on di(benzothienyl)perfluorocyclopentene **44** (Schemes 15 and 16).

Unlike Scheme 15, which shows the synthesis of symmetrical products **45** and **46**, Scheme 16 illustrates the approach to the synthesis of unsymmetrical photochromes **49** and **50** starting from mononitro derivative **47**, prepared in 75% yield from **44** (in a mixture with dinitro derivative **48**).
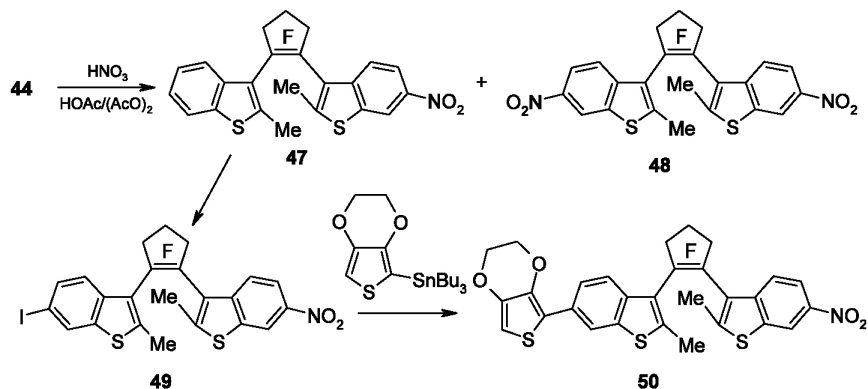
Scheme 16
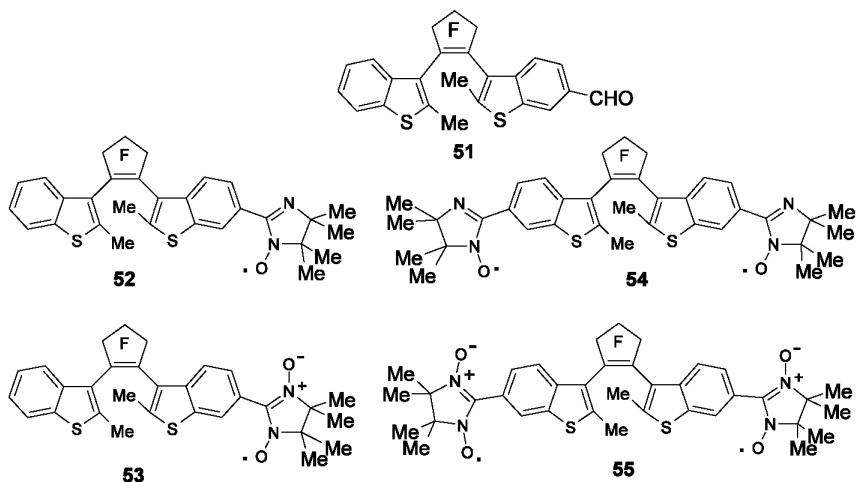
A similar approach was used for the synthesis of dihetarylethenes containing imino nitroxide and nitronyl nitroxide radicals (05OL3777), as well as of bis(benzothienyl)perfluorocyclopentenes containing one or two chryso[*b*]thiophene rings (04T9863). In this case, the initially synthesized diiodide **45** (Scheme 15) is treated with butyllithium and dimethylformamide, and the resulting formyl derivatives **46** (39%) and **51** (14%) are separated by column chromatography.

Subsequent treatment of the aldehydes affords diradicals **52–55** and chryso[*b*]thiophenes **56** and **57**.

R = H, COMe, COOMe
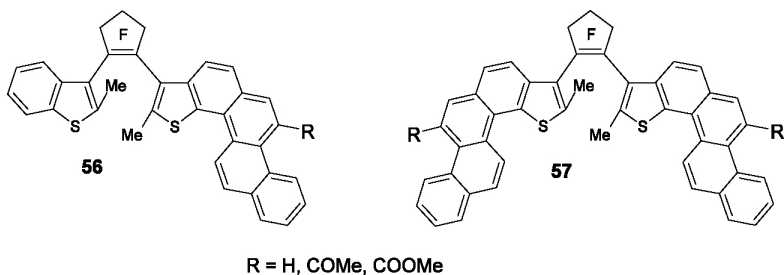
In 05JOC5545, unsymmetrical acetylene derivatives **58** and **59** were described.
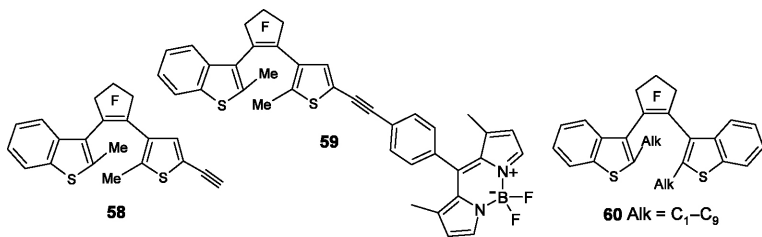
In a series of studies, substituents were introduced or varied at the 2-positions of the thiophene rings of di(benzothienyl)ethenes. The reactions of 3-bromo-2(*n*-alkyl)-1-benzothiophene with BuLi and octafluorocyclopentene gave bis(2-*n*-alkyl-1-benzothiophen-3-yl)perfluorocyclo-pentenes **60** containing alkyl substituents with a different chain length at position 2 of the benzothiophene ring. The authors stated that the Et-, Pr-, and Bu-containing derivatives exhibit photochromic properties even in the crystalline state (06JPP(A)162).

As mentioned in Scheme 3, in spite of the presence of the benzothiazole rings at positions 2 and 2′ of the thienyl moieties in compound **5**, the latter exhibits photochromic properties. Compound **61** was synthesized under similar conditions, and was shown also to have photochromic properties (01RCB110) (Scheme 17).

The same approach was used for the preparation of photochromic dihetarylethenes **63** containing the phenylethynyl and 1-pentynyl groups at the reactive carbon atom (04TL1155). Bromide **62** was synthesized by the Sonogashira reaction of 2,3-dibromobenzo[*b*]thiophene with ethynylbenzene or 1-pentyne (01T7871), and the subsequent reaction of compound **62** with octafluorocyclopentene afforded the photochromes (Scheme 18).
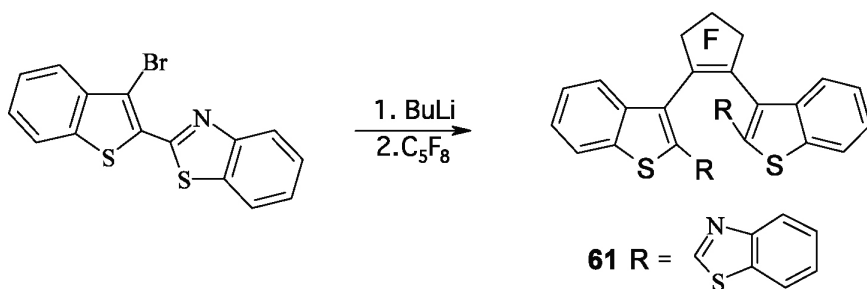
Scheme 17
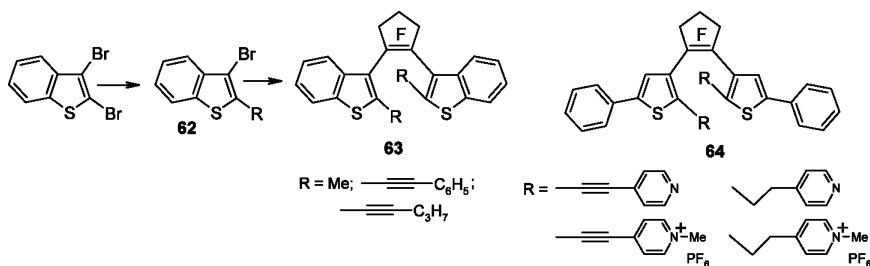
Scheme 18
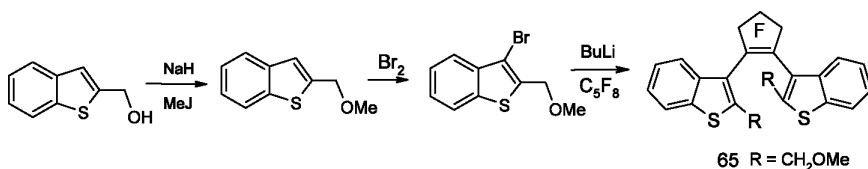
Scheme 19

More recently, dithienylethenes **64** containing the (4-pyridyl)ethyl and (4-pyridyl)ethynyl groups at position 2 of the thiophene ring (08OL2051) have been synthesized in a similar way.Photochrome **65** was prepared from 2-hydroxymethylbenzo[*b*]thiophene according to Scheme 19 (05IZV2697).

Because it is much easier to obtain derivatives containing lithium at position 3 of the thiophene ring compared to the replacement of halogen in the benzene ring, it became possible to synthesize photochrome **66**, in which the chlorine atom preintroduced into the benzene ring remains intact (07MC125) (Scheme 20).

The oxidation of dihetarylethene **44** with *m*-chloroper-benzoic acid (*m*-CPBA) in CH$_2$Cl$_2$ afforded 1,1-dioxide **67** (06T5855, 073173, 08CC4622, 09JMC97) in yields up to 90%; in the case of the 6-acetyl derivative, the yield of bis-sulfone **68** was only 35% (06T5855) because of a Baeyer–Villiger oxidation side reaction of the carbonyl group. Protection of the latter as the dioxolane derivative made it possible to increase the yield of **69** to 72% (Scheme 21).

Photochromic sulfones **67** (R = CH$_3$, C$_3$H$_7$) can be encapsulated into iron oxide particles to form unique multifunctional nanosystems having, for example, fluorescence, magnetic, and flocculation properties (08CC4622).

The synthesis of photochromic compounds containing combinations of benzothiophene and thiophene **70** (04JPP(A)97, 09JMS100), indene **71** (06TL1267), or benzofuran rings **72** and **73** (06BCJ1100, 08BCSJ644) was documented (Scheme 22).
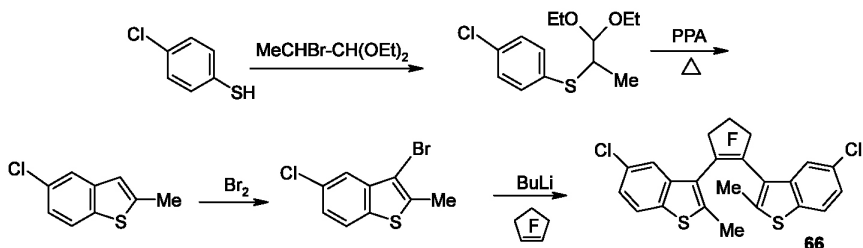
Scheme 20
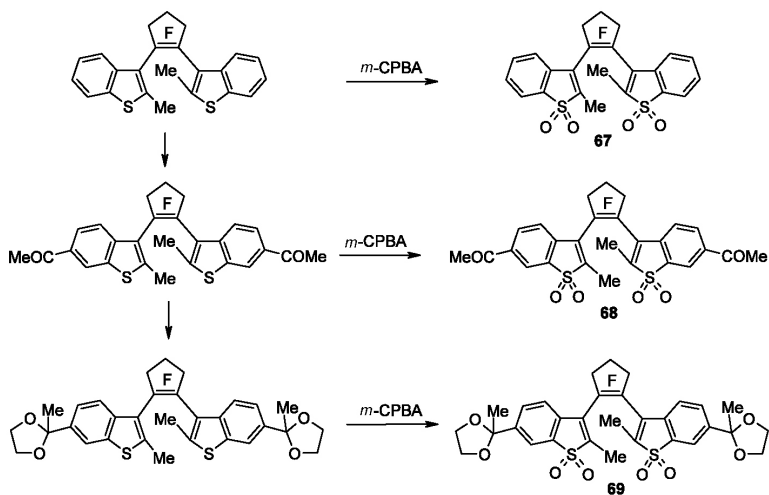
Scheme 21
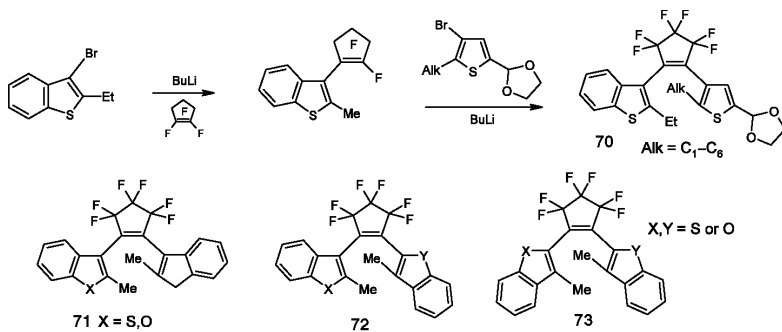
Scheme 22

Photochromic dendritic polymers **74** considered as optical memory elements were characterized (08CC5755).
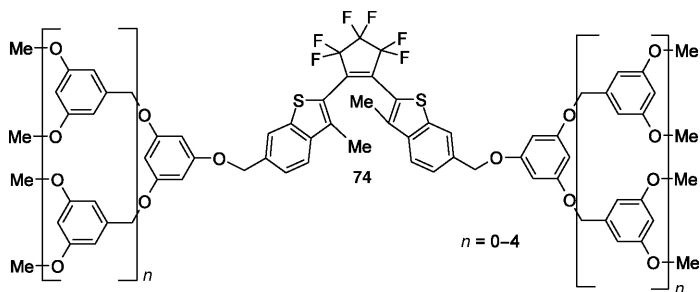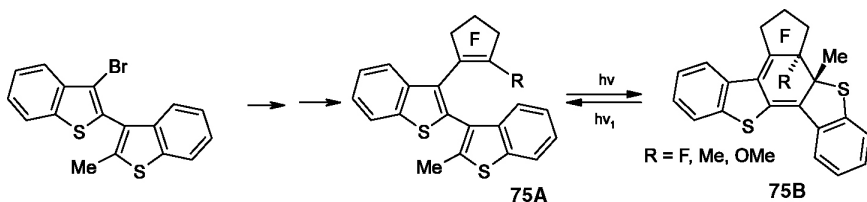
Scheme 23
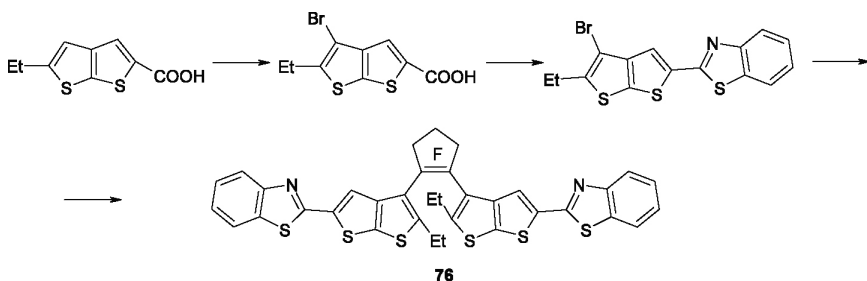
Scheme 24

The synthesis of photochromic 6π conjugate systems having a bis(2,3'-benzothienyl) unit **75** was described (04CC1010) (Scheme 23). These systems have unusual structures, in which the fluorine atom, the methyl group, or the trifluoromethyl group rather than the heterocycle is located in a vicinal position adjacent to the benzothienyl substituent in the perfluorocyclopentene moiety.

In a series of studies, perfluorinated derivatives containing thienothiophene substituents were prepared. Thus, the synthesis of **76** (Scheme 24) was documented in 05KGS360. The synthesis of its isomeric analogs **77** and **78** (Scheme 25) was described in 01RCB110.

The authors mentioned that lithium can migrate in the case of direct metallation of the precursor bromide or in the resulting photochrome **78** with R = H, as evidenced by the presence of **79** among the products (01RCB110) (Scheme 25).

The only example of the synthesis of photochromic perfluorocyclopentenes **80** containing dithienothiophene substituents (Scheme 26) was given in the study (02IZV1942).
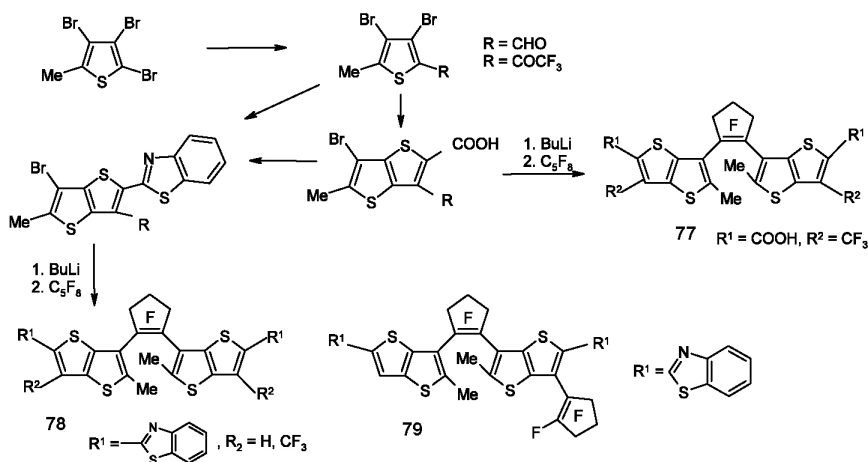
Scheme 25

2.1.32. Other heterocycles and "hybrids"

Photochromes can be prepared by the reactions of perfluorocyclopentene not only with lithium derivatives of thiophene but also with other heterocycles, in particular, with thiazole (Scheme 27). Generally, the yields of thiazole derivatives are substantially lower than those of the thiophene series and the above-described fused products (92JOC3726, 98T6627, 07JMC4414, 09AM309). The oxidation of 1,2-bis[5'-methyl-2'-(2''-pyridyl)thiazolyl]perfluorocyclopentene **81** with *m*-CPBA affords the corresponding photochromic mono- and bis-*N*-oxides exhibiting photochromism both in solution and in the crystalline state (09TL1485).

Scheme 26

Scheme 27

82   R = Me, Bu, Ph   **83**   **84**   X,Y = H, I, CHO, NO$_2$, Ph; R=Me
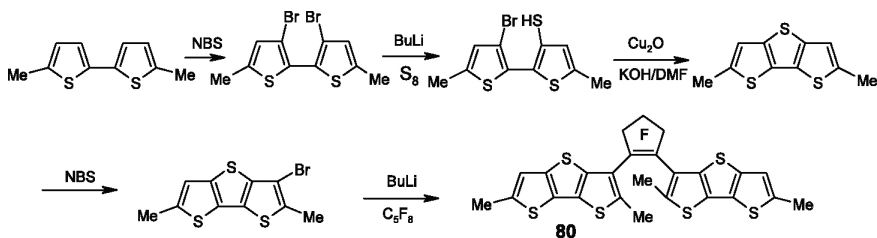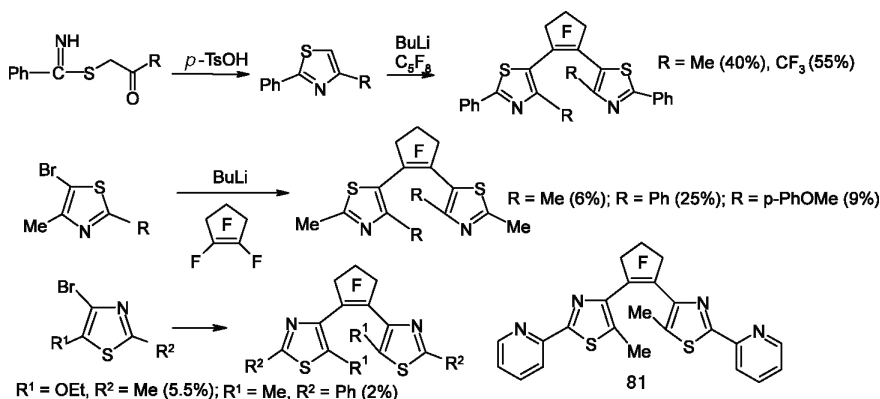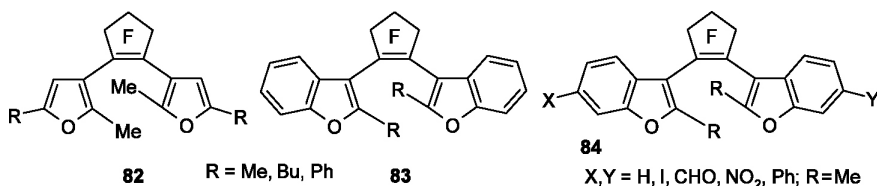
The reaction of 2,5-disubstituted 3-furyl bromides with butyl-lithium and octafluorocyclopentene in dry tetrahydrofuran (THF) at −78°C gave bis(furyl)ethenes **82** (06JMC4690). Photochrome **83** (05JOC10323, 06EJO3105) (29–46% yield) and a series of its derivatives **84** (55–65%) containing different substituents at position 6 of the benzofuran ring were synthesized from 3-bromo-2-methyl-1-benzofuran (08JPP(A)146).

1,2-Dihetarylethene **86** containing two pyrrole rings was prepared in 11% yield by the successive reactions of the corresponding bromide **85** with BuLi and C$_5$F$_8$ in THF (99CL835) (Scheme 28). More recently, French researchers (03NJC1425) optimized the reaction conditions, resulting in an increase in the yield to 74%, and synthesized a large series of symmetrical and unsymmetrical 5,5′-disubstitued derivatives **87**.

Dibromo-substituted dipyridylethene **88** was prepared in 67% yield from the known 2,6-dibromo-3,5-dimethylpyridine. The latter can easily be converted into various derivatives **89** through halogen–metal exchange followed by a reaction with electrophiles or through one of the numerous cross-coupling reactions involving aryl halides (05MI1) (Scheme 29).
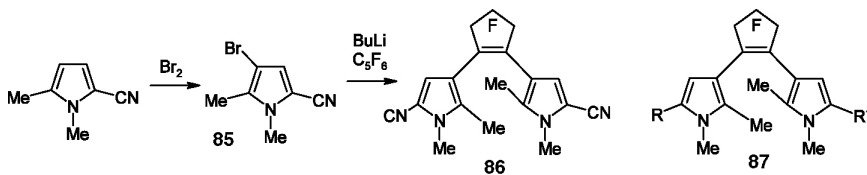
Scheme 28
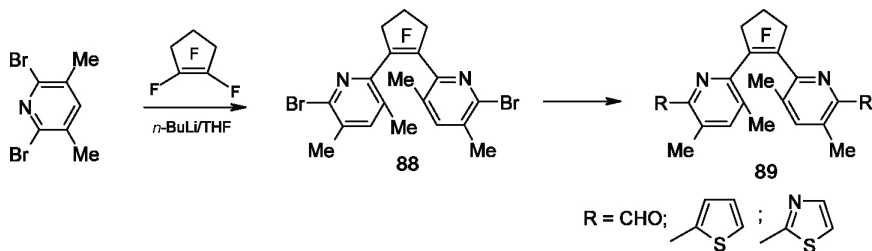
Scheme 29

"Hybrid" 1-hetaryl-2-thienylperfluorocyclopentenes containing the thiazole **90** (04T6155) (Scheme 30), pyrrole **91** (07OL2139), imidazole **92** (09CEJ1577), or pyrazole **93** (06TL6473) rings were described.

Nontraditional photochromes with high absorption coefficients of the colored isomers **94B** and **95B** are worthy of notice. These compounds were synthesized from 2-bromo-3-methyl-2-butene and 4-bromo-5-methyl-2-phenylthiazole, respectively, with BuLi and the corresponding mono-fluorides (05MI2467) (Scheme 31).
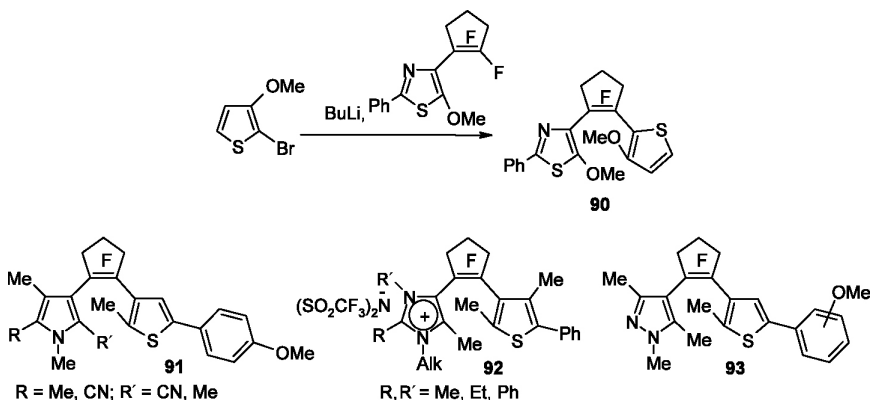
Scheme 30
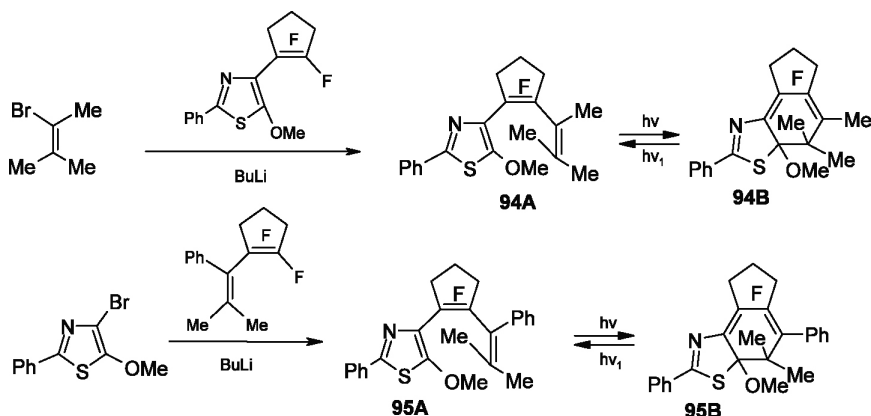
Scheme 31

The synthesis of diarylethenes from hetaryl bromides and octafluoro-cyclopentene using a microflow system allows the preparation of various symmetrical and unsymmetrical diarylperfluorocyclopentenes in 47–87% yields at 0°C (07CC2947).

2.1.4 DTEs with repeating photochromic fragments

Recently, the synthesis of photochromic compounds containing two or more diarylethene fragments bound either directly or through linkers has been performed. Scheme 32 illustrates one approach to **96** containing two hexafluorocyclopentene-bridged dihetarylethene fragments (05JACS8922).

1,2-Bis(5-chloro-2-methylthien-3-yl)perfluorocyclopentene with *n*-butyllithium and octafluorocyclopentene in diethyl ether at −78°C gave
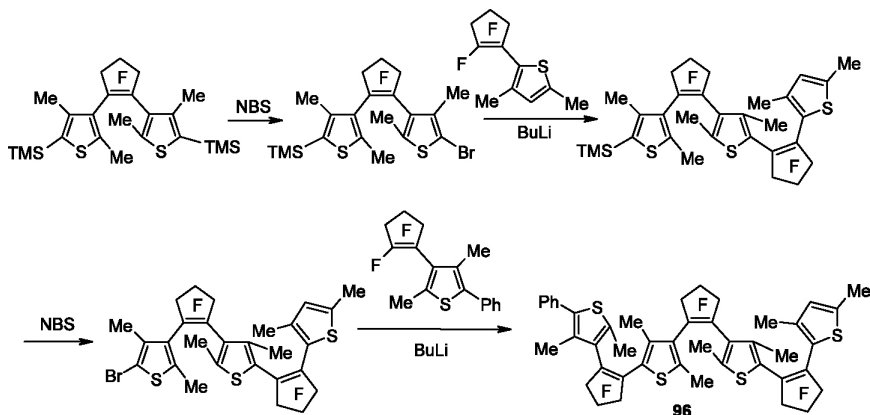
Scheme 32
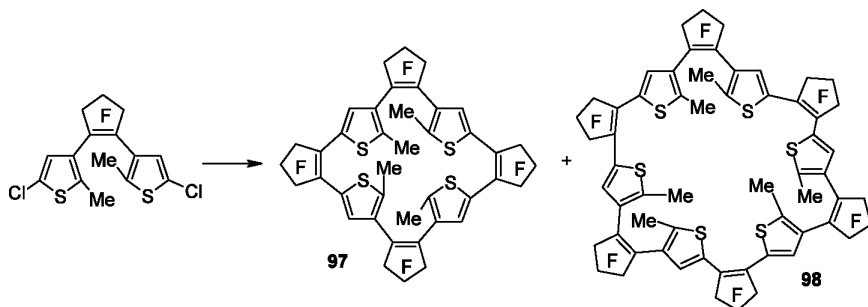
Scheme 33

macrocyclic **97** (8.4%) and **98** (2.6%) (08TL1582) (Scheme 33). The authors noted that **97** does not exhibit photochromic properties because its cyclic form is conformationally unfavorable because of the formation of the strained 20-membered ring, whereas 30-membered macrocycle **98** is a typical photochrome.

New macromolecules **99** and **100** can easily be synthesized in four steps from 1,2-bis(5-bromo-2-methyl-3-thienyl)perfluorocyclopentene by the Sonogashira coupling reaction (05T12256).
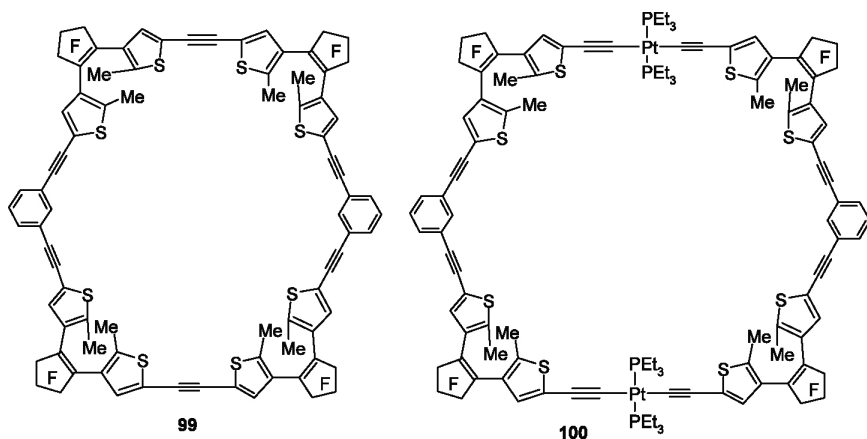
Scheme 34 shows the synthesis of **101**, in which two photochromic fragments are separated by the phenyl ring (03T8359).

Fluorene **102** (04BCJ945) and products **104**, prepared by the electro-chemical dimerization of photochrome **103** (09OL721), are given in Scheme 35.

Photochromic "dendrimers" **105** (07CL888), **106** (04CL1380), and **107** (06T9059), prepared from compounds **108** and **109**, respectively, were described.
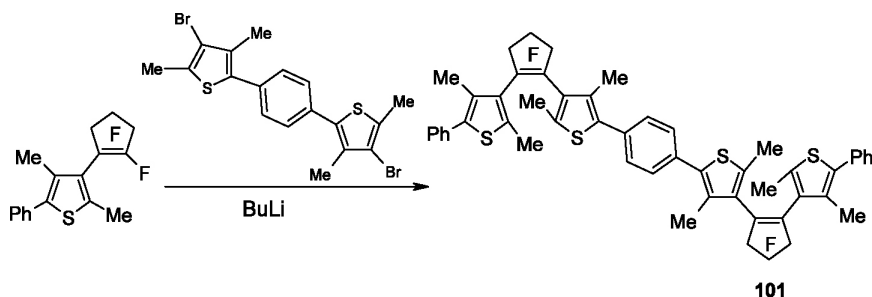
Scheme 34
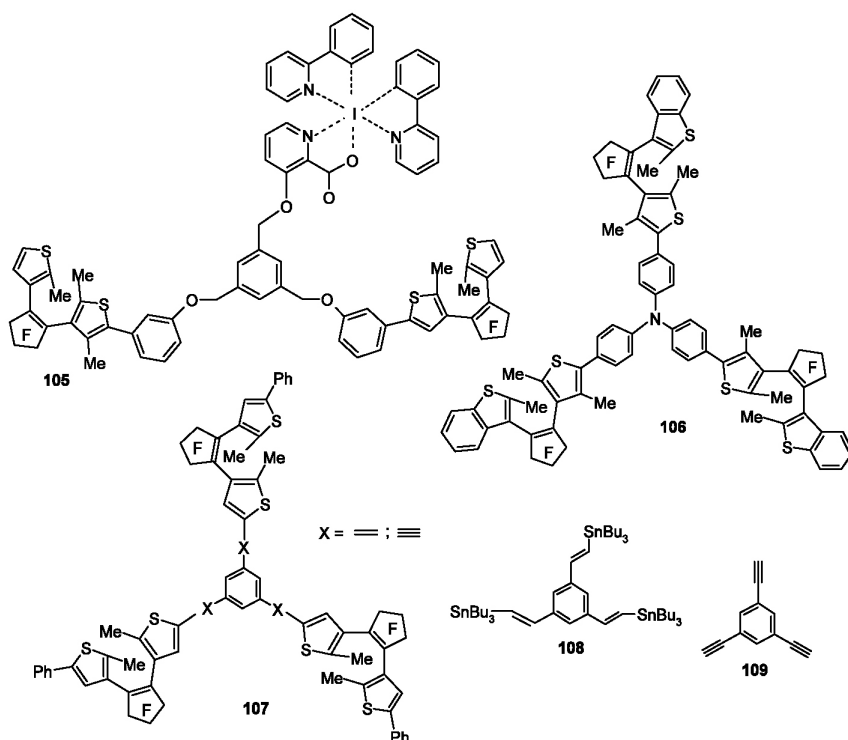
In 09NJC1320, an original method was developed for the preparation of fluorescent photochrome **112**, which contains both electron-donating and electron-withdrawing groups and bipyridine-bridged dithienylethene fragments, from **110** with bisphosphonate bipyridine **111** in the presence of a base (Scheme 36).

Biphotochromic "dyads" containing dithienylperfluorocyclopentene and spiropyran (naphthopyran) fragments (05AG(E)5048, 05T3719) are
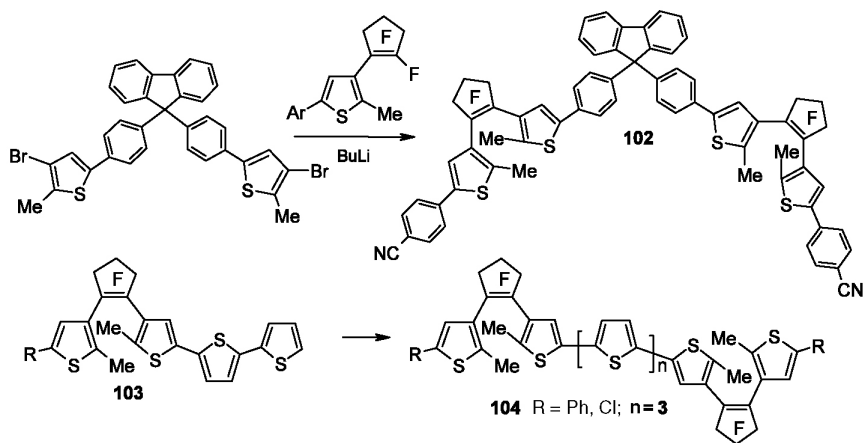
Scheme 35
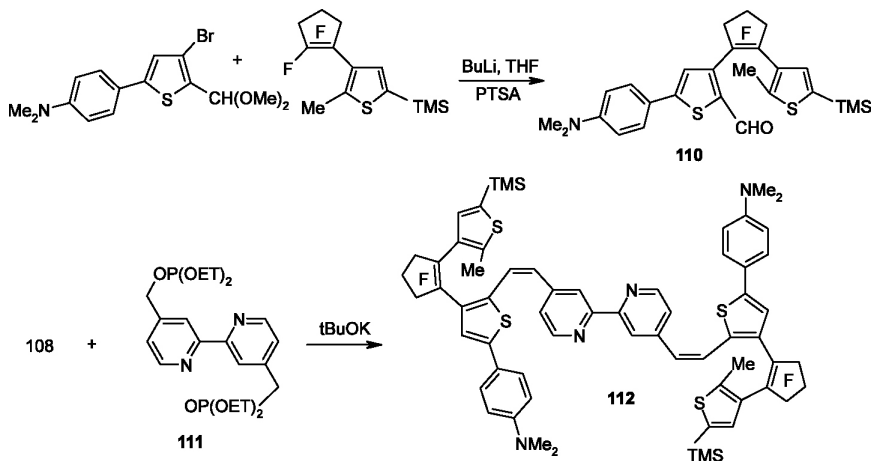
Scheme 36

of interest. Dyad **113** was synthesized from 1,2-bis[5-(4-hydroxyphenyl)-2-methyl-3-thienyl]perfluorocyclopentene with 1′-(5-bromopentyl)-3′,3′-dimethyl-6-nitroindolinospirobenzopyran in the presence of K_2CO_3 and crown ether in acetone; biphotochromic **115**, in which, unlike compound **113**, the photochromic fragments are directly linked to each other, was synthesized in 52% yield from chromene **114** (05AG(E)5048) (Scheme 37).

113
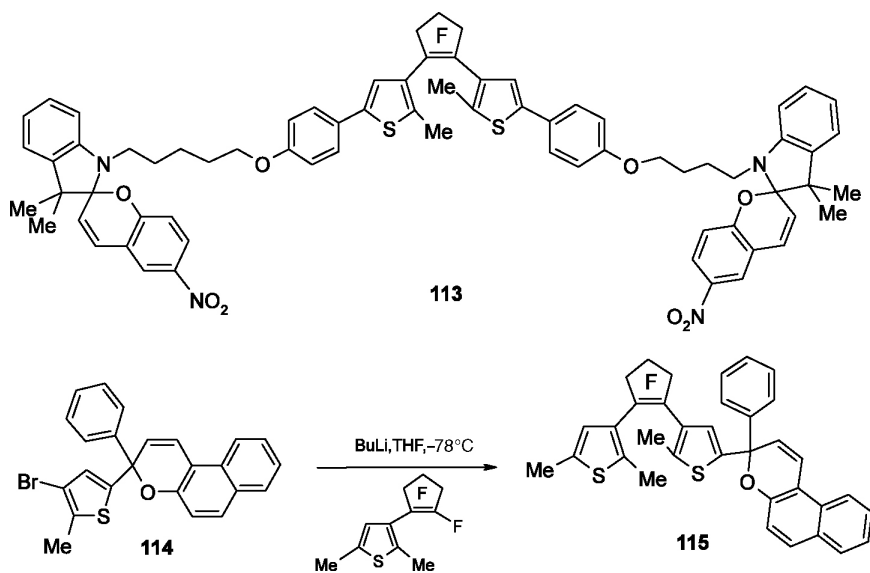
Scheme 37

2.2 McMurry reaction

Usually thermally irreversible photochromes with high fatigue resistance can be prepared using perfluorocyclopentene. However, the latter reactant is relatively expensive and uneasy to handle because of its high volatility (bp 26–28°C) (97MI1). Moreover, many reactions give final products in low yields. This stimulated the search for new approaches to photochromes containing the hexafluorocyclopentene fragment. Thus, Feringa and coworkers developed a method for symmetrical derivatives of 1,2-dithienyl-perfluorocyclopentene based on the relatively available diethyl hexafluor-oglutarate as the starting compound (Scheme 38) (99TL1775, 03EJO155). The formation of dithienyl diketone **116** and the cyclization to the final product **117** (the McMurry reaction) occur in 70 and 55% yields, respectively (Scheme 38).

Product **117** is a convenient starting compound for the subsequent modification of photochromes. Publication (09TL1614) gives an efficient synthetic route to both symmetrical **118** and unsymmetrical **119** phenyl-substituted dihetarylethenes bearing amino, hydroxy, or carboxy groups based on a Suzuki reaction of dichloride **117** with commercially available substituted boronic acids (or their pinacol esters) in a dimethyl ether (DME)–H$_2$O mixture (4:1). For the symmetrical products, the yields are 85–95%; for the unsymmetrical products, they are 60%.
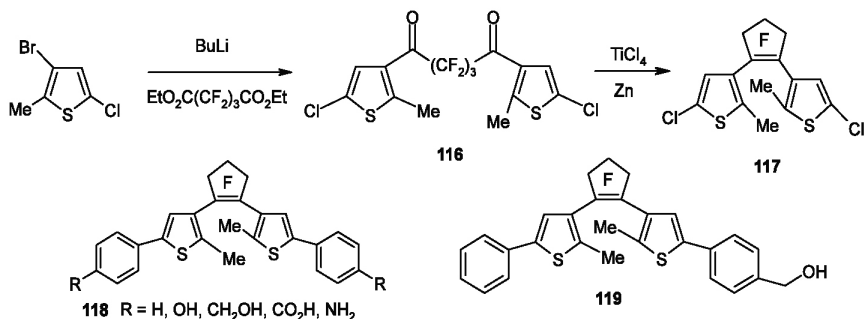
Scheme 38

3. SYNTHESIS OF DITHIENYLPERHYDROCYCLOPENTENES AND THEIR HETEROANALOGS

3.1 *Perhydrocyclopentenes*

Recently, active research on the synthesis of photochromes containing the central perhydrocyclopentene fragment, a promising alternative to dithienylperfluorocyclopentenes, has been performed. Scheme 39 shows a convenient general approach to these compounds starting from 2-chloro-5-methylthiophene developed in 1998 by Lucas et al. (98CC2313). The first step involves the Friedel–Crafts acylation of 2-chloro-5-methylthiophene with glutaryl dichloride. The subsequent McMurry cyclization of the diketone **120** affords cyclopentene **121** in 44% yield (89CRV1513).
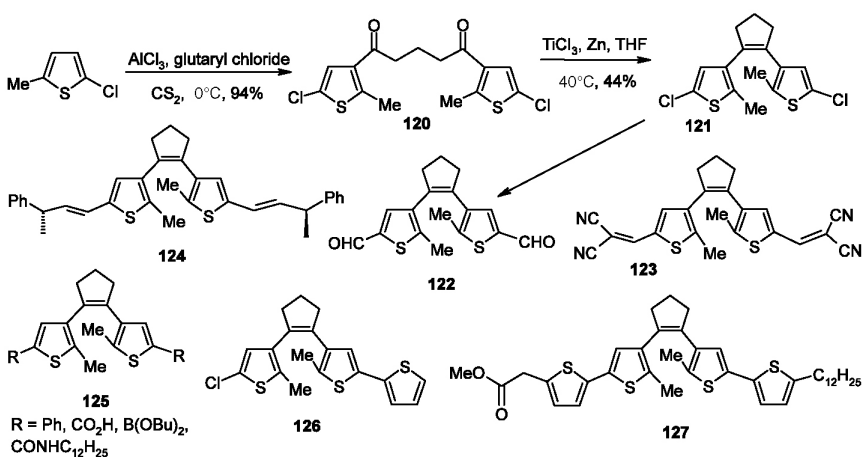
Scheme 39

The McMurry reaction (the reductive dimerization of carbonyl compounds giving olefins after treatment with the low-valent titanium reagents TiCl$_3$/Mg and TiCl$_3$/Zn in THF at 40°C) (CR891513) is a key step in the synthesis of photochromic cyclopentene derivatives. Later, it has been shown that TiCl$_4$, which is easier to handle than TiCl$_3$, can be used. The cyclization products are formed in 50–60% yields (98S1092, 03EJO155). The advantages of this method are that the reactions can be scaled and inexpensive starting materials can be used.

The chlorine atoms in the key starting **121** can be easily replaced by metal in the presence of BuLi at 20°C, which offers considerable promise in preparing various symmetrical and unsymmetrical derivatives. In solution, this product exhibits typical photochromic properties. However, an X-ray diffraction study of **121** showed that the thiophene rings in the molecule are parallel to each other, which is responsible for the absence of the photochromic properties in the crystalline state (05AC (E)o951).

The transformations of **121** into various symmetrical and unsymmetrical perhydrocyclopentene-bridge photochromes, for example, **122–127**, were documented (98CC2313, 03EJOC155, 04CSR85, 07CC1698).

The review (09RCR329) gave numerous examples of the recently synthesized compounds with various useful properties, such as water-soluble salts of 1,2-bis[2-methyl-5-(4-pyridinium)-3-thienyl]cyclopentene-*N*,*N'*-bisacetic acid (06CC2147), photosensitive organogelators containing urea fragments (05JA13804, 08OBC1544) and bearing cholesterol groups (06CC1497) or coumarin components (08OBC1268), fluorescent photochromes suitable for the data reading and storage (06CM235, 07JPP(A)07), chelate compounds exhibiting fluorescence in the closed form (04AM2104, 09OL161), and mono- and bis-*S*-acyl derivatives (05MI4, 06CC3597, 09NL76) for the synthesis of gold nanoparticles, etc.

Product **128**, which undergoes reversible photo- and electrochemical transformations, was described in 06CC3930, where electrochemical transformations provide a nondestructive electrochemical readout.

128   **129**
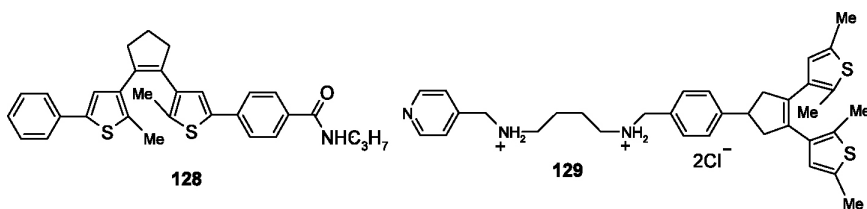
Product **129** containing a cyclopentene-based photochromic fragment was proposed as an "axis" of pseudorotaxane structures, which has potential for use in the construction of a prototype of molecular machines active as a functional stopper (08DP294).
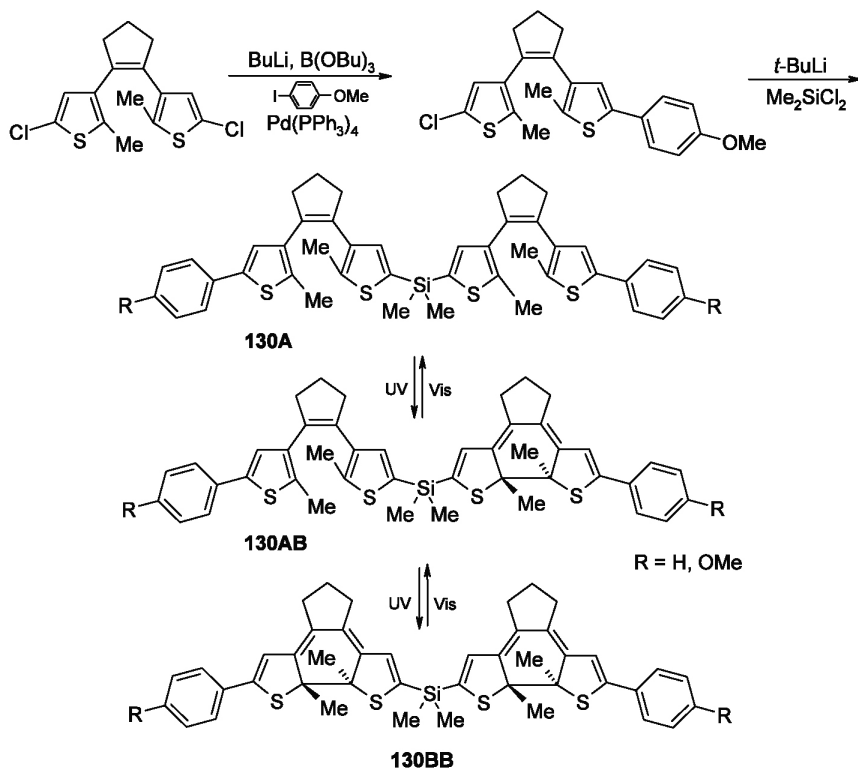
Scheme 40

Feringa and coworkers (07OBC1170) constructed two-component molecular switches **130** based on photochromic dithienylcyclopentenes covalently bound through the silicon atom starting from dichloro derivative **121** (Scheme 40).

The corresponding bis(benzothienyl)perhydrocyclopentene **131**, which was synthesized from 5-chloro-2-methylbenzo[*b*]thiophene similarly to dithienylcyclopentenes, was subjected to subsequent modifications due to the presence of chlorine atoms in the benzene ring (07MC125) (Scheme 41).

Another original method was developed for the cyclopentene fragment based on the use of dithienylbicycloheptadiene derivatives **132** in a ring-opening metathesis polymerization (ROMP) with ethyl vinyl ether and affords the corresponding polymeric photochromes **133** containing the dithienylcyclopentadiene fragment in the main (04AM123) or side chain (00OL2749, 05CM5473). Commercially available bis(tricyclohexyl-phosphine) benzylidene ruthenium(IV) dichloride is the polymerization initiator (Scheme 42).
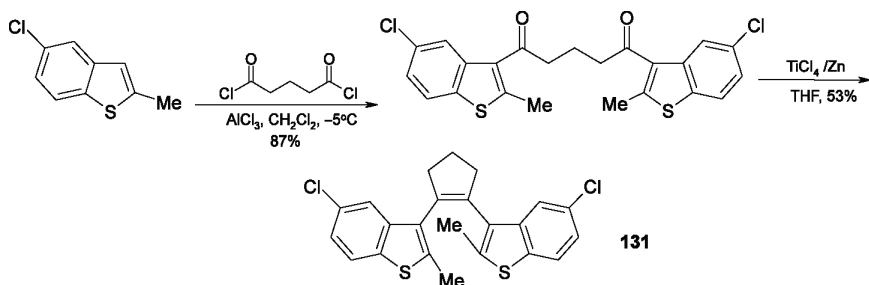
Scheme 41
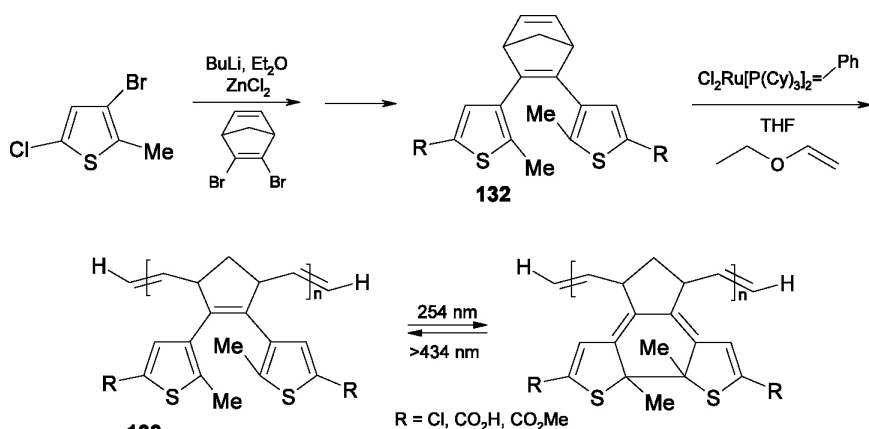
Scheme 42

A comparative analysis of the spectroscopic and photochromic properties of dithienylperhydro- and perfluorocyclopentenes were reported in 03EJO1887 and 05JPC9437. Their photochromic properties are similar, but the perhydro derivatives were shown to be thermally and photochemically less stable.

3.2 3,4-Dithienyl-2,5-dihydrothiophenes

The synthesis of dithienylethenes bound to heteroanalogs of cyclopentene, in particular to the 2,5-dihydrothiophene ring, also deserves notice. Diketone **135** was prepared by the replacement of the bromine atoms in two molecules of **134** by the sulfide anion followed by the McMurry cyclization to form thiacyclopentene derivative **136** (03OL1435). Diiodide **137** is also successfully used as the synthon for the subsequent functionalization; this compound is involved in the Suzuki reaction to
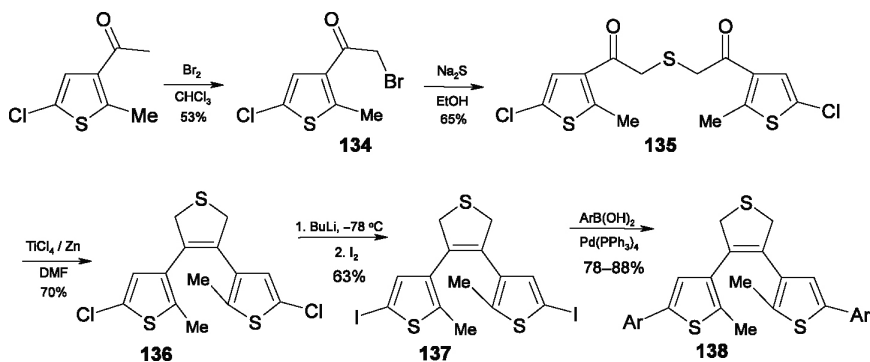
Scheme 43

give various aryl-substituted **138** in high yields (06SL737, 07JEC27) (Scheme 43).

Fluorescent dihetarylethenes **140** and **141** were synthesized based on 5,5′-diformyl derivative **139** and phenanthroquinone or substituted benzyl and ammonium acetate in acetic acid (07JMC861) (Scheme 44).

2,5-Dihydrothiophene-   and   2,5-dihydrothiophene-1,1-dioxide-bridged **142** and **143** are based on thieno[3,2-*b*]pyrrole (02OL3879, 03ZOR1725) (Scheme 45).

3.3 3,4-Dihetaryl-2,5-dihydropyrroles

The McMurry reaction also gave new multiphotochromic dithienylethenes **145** and **146** containing an N-substituted dihydropyrrole bridge
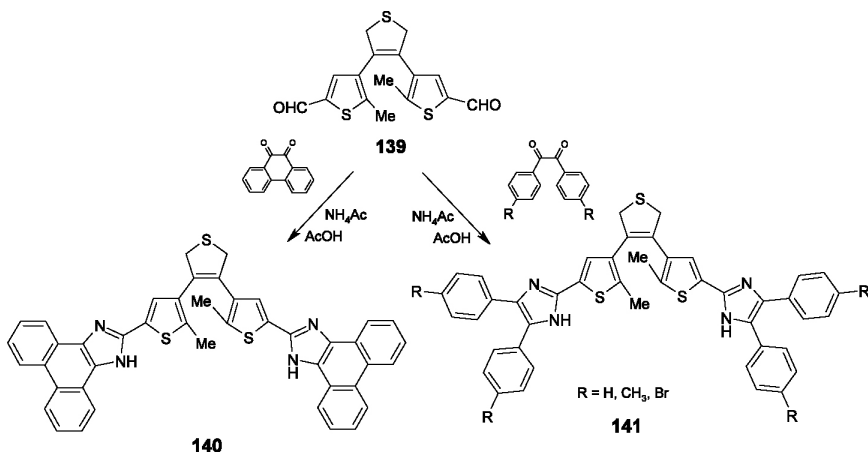
Scheme 44
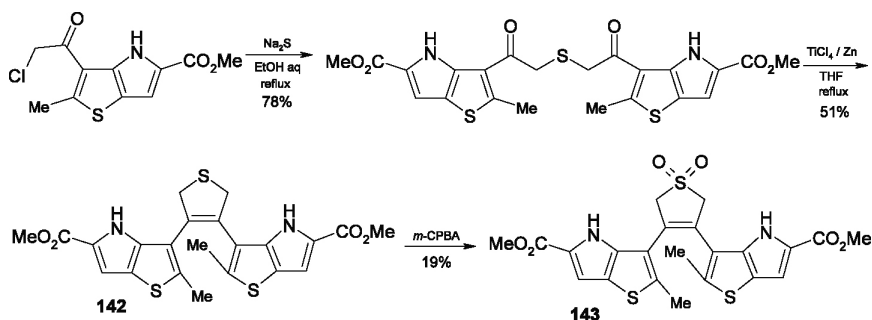
Scheme 45

starting from the corresponding 3-aza-1,5-diketone **144** (05CCL175, 06CJC264) (Scheme 46).
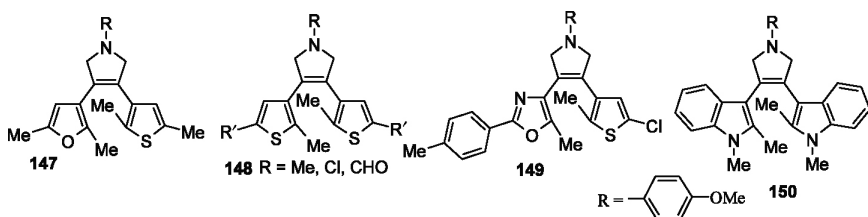
A series of symmetrical and unsymmetrical photochromic 3,4-dihe-taryl-2,5-dihydropyrroles **147–150** containing the furan, thiophene, oxa-zole, or indole rings were synthesized as described above in 60–80% yields starting from *p*-anisidine (05JOC5001).
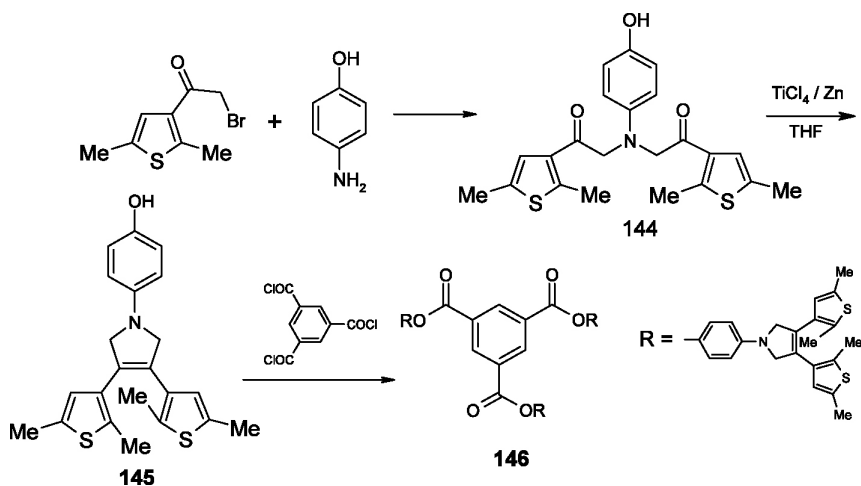
Scheme 46

Finally consider the syntheses of structurally similar compounds, carried out not by McMurry reactions but according to other procedures. For example, benzothiophene-bridged system **151** was prepared according to Scheme 47 from 2,3-dibromobenzothiophene and 3-methyl-2-thienylmagneisum bromide in 23% yield (08OL3639). Bis-sulfone **152** prepared from this photochrome does not exhibit photochromic properties, whereas its benzothiophene analog **153** is a typical photochrome (09TL5288), such as dihetarylethenes **154** and **155**.

A new class of photochromic diarylethenes containing thieno[3,2-*b*] thiophenes, dithieno[3,2-*b*:2′,3′-*d*]thiophene (08CC5203), and dithieno [3,2-*b*:2′,3′-*d*]pyrroles (09CEJ10005) with photoswitchable luminescence properties were synthesized by Suzuki cross-coupling reactions (Scheme 48).
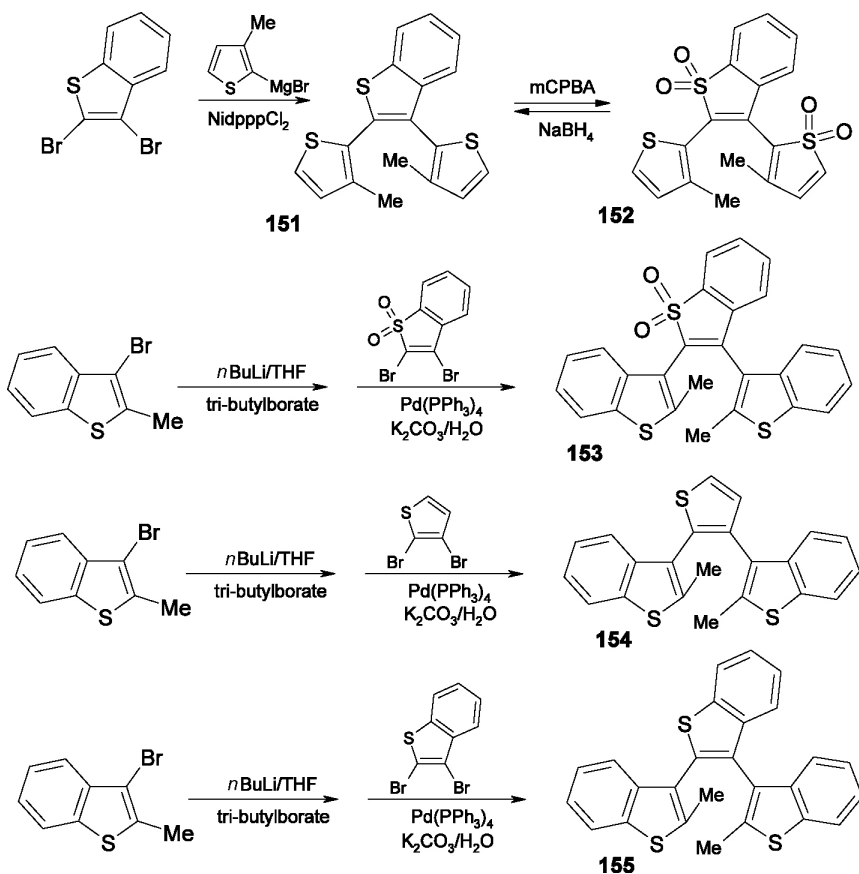
Scheme 47

Scheme 48
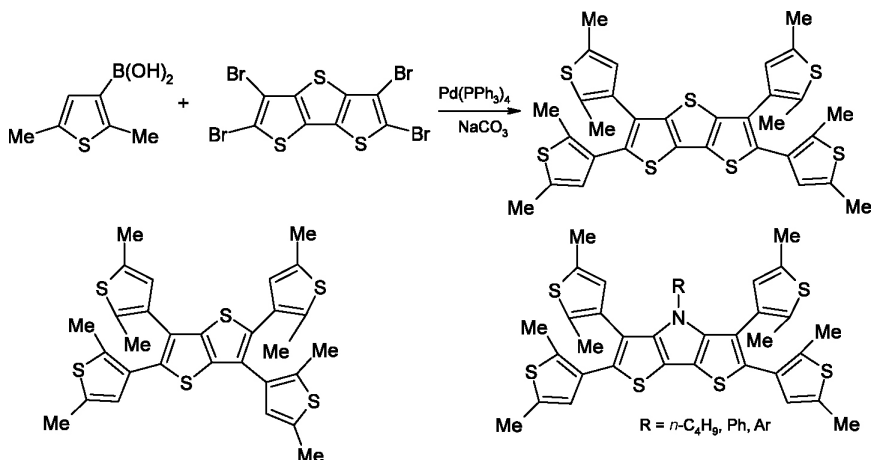
Recently (08JPCA4765), new thermally irreversible photochromes **156–159** containing silicon or phosphorus atoms in the five-membered bridge have been synthesized. They have fluorescence in the closed forms, whereas their open forms do not exhibit fluorescence. Hence, they are highly promising for the nondestructive readout of optical information (07MI1). Their synthesis from 2- and 3-substituted butadienes was documented (09NJC1357).
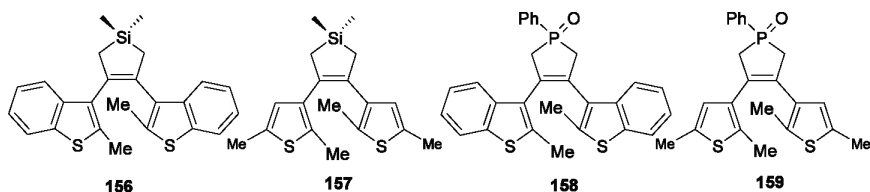
4. DITHIENYLMALEIC ANHYDRIDES

The synthesis of dithienyl photochromes containing a maleic anhydride fragment (a furan-2,5-dione fragment) as the ethene bridge was a difficult problem. Initially, vicinal dinitriles **160** and **162** were used as the starting compounds (Scheme 49). But the latter compounds give a maleic anhydride only in the *cis* conformations. The separation of the *cis* and *trans* isomers is an additional time-consuming laborious problem.

1,2-Dicyano-1,2-bis(2,3,5-trimethylthiophen-3-yl)ethene **160**, prepared in 47% yield, was hydrolyzed in an alkaline solution to form maleic
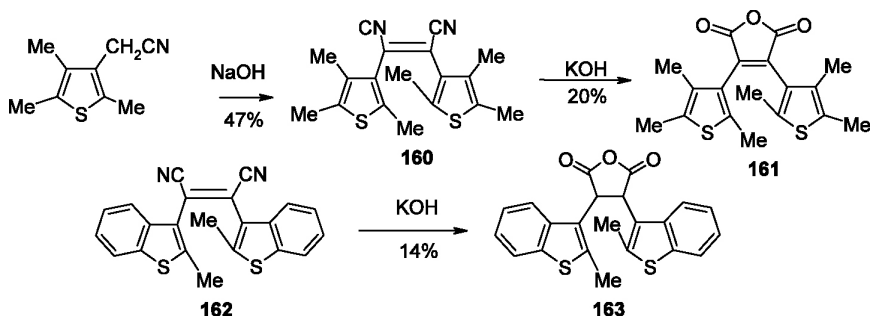
Scheme 49

anhydride derivative **161** (88JOC803) whose total yield based on the starting trimethylthiophene is low (about 4%).

The cyclization giving maleic anhydride derivative **163** is also characterized by low yield. Moreover, the total yield of the starting dicyanide **162** was about 25% based on 2-methylbenzothiophene (90BCJ1311). This inefficiency was typical of most of the syntheses of photochromic maleic anhydrides from nitriles. Hence, the development of more efficient methods is a very important problem. Anhydride **163** has been synthesized recently (08JACS7286) by the Perkin reaction in good yields in each step (Scheme 50).

In 01KGS81, an original method for the synthesis of photochrome **165** was described (Scheme 51). The first step involves the generation of 1,2-bis (2,5-dimethylthien-3-yl)cyclobutene-3,4-dione by the acylation of 2,5-dimethylthiophene with 1,2-dichlorobutene-3,4-dione in the presence of aluminum chloride and pyridine (00KGS261). Then the Baeyer–Villiger oxidation of the resulting diketone **164** with 90% hydrogen peroxide in acetonitrile (95% yield) or with 35% H_2O_2 in CH_3CN in the presence of a catalytic amount of p-toluenesulfonic acid occurs (89% yields). Curiously, although dione **164** does not exhibit photochromic properties, its cyclic acetals (ketals) (07OL1915) are photochromes.

This method has a general character, and was successfully applied to the synthesis of photochrome **166** containing fused thieno[3,2-b]thiophene
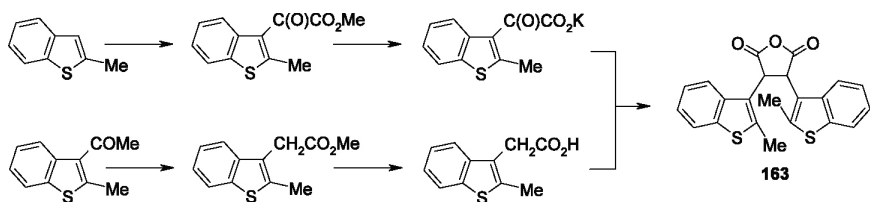
Scheme 50
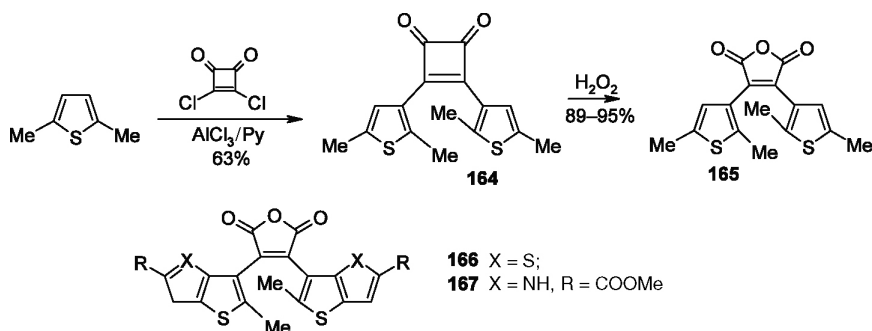
Scheme 51

fragments (02IZV1396), as well of 4*H*-thieno[3,2-*b*]pyrrole derivatives **167** (02ZOR1386). Since squaric acid chloride is a commercial reagent, this approach makes the synthesis of photochromes containing the maleic acid fragment as the ethene bridge relatively easy.

A simple method for the synthesis of maleic anhydride derivative **165** starting from 2,5-dimethyl-3-thienylboronic acid and commercially available inexpensive mucobromic acid **168** was reported (04IZV2238) (Scheme 52). The starting boronic acid was prepared in good yield from 2,5-dimethyl-3-iodothiophene.

Acid chlorides **168** and **171** with thienylglyoxalic acid **169** in the presence of triethylamine gave 3-(3-coumarinyl)-4-(3-thienyl)maleic
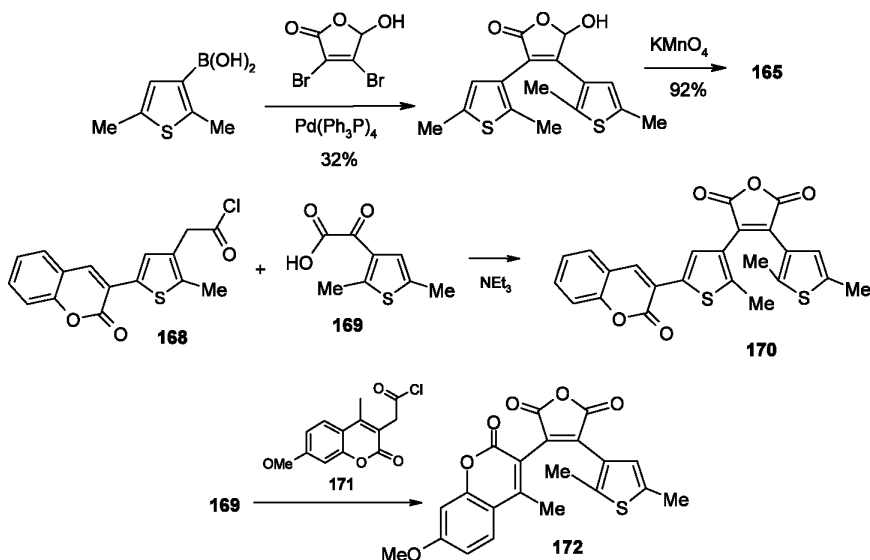
Scheme 52

anhydride **170** and thienyl(coumarinyl-thienyl)maleic anhydride **172**, respectively (08ZOR600).

Recently, a new method was developed for the synthesis of both symmetrical and unsymmetrical derivatives of dithienylmaleic anhydride **165** and **173–176** based on the condensation of thienylacetic acid with halo ketones **168** and **171** at 70–90°C. The key feature occurs in the presence of atmospheric oxygen acting as an oxidant for the intermediate lactones (10RUP2378273) (Scheme 53).

Structurally similar photochromic maleic anhydride derivatives **177** with a similar reaction mechanism were prepared by Irie (05CL64) by a one-pot synthesis from 2-methoxybenzothiophene, oxalyl chloride, and pentene-3-carboxylic acid (3-pentenoic acid) in dichloromethane in the presence of triethylamine at 5°C for 2 h according to Scheme 54.

5. DITHIENYLMALEIMIDES

The syntheses of photochromes in which the heterocycles are separated by the maleimide ring described in the literature were as time-consuming as the syntheses of compounds based on maleic anhydride. A general approach to these photochromes is exemplified in Scheme 55 using unsymmetrical photochrome **180** (98BCJ1101). Here, the treatment of 2-methoxybenzothiophene with oxalyl chloride and aminoacetonitrile
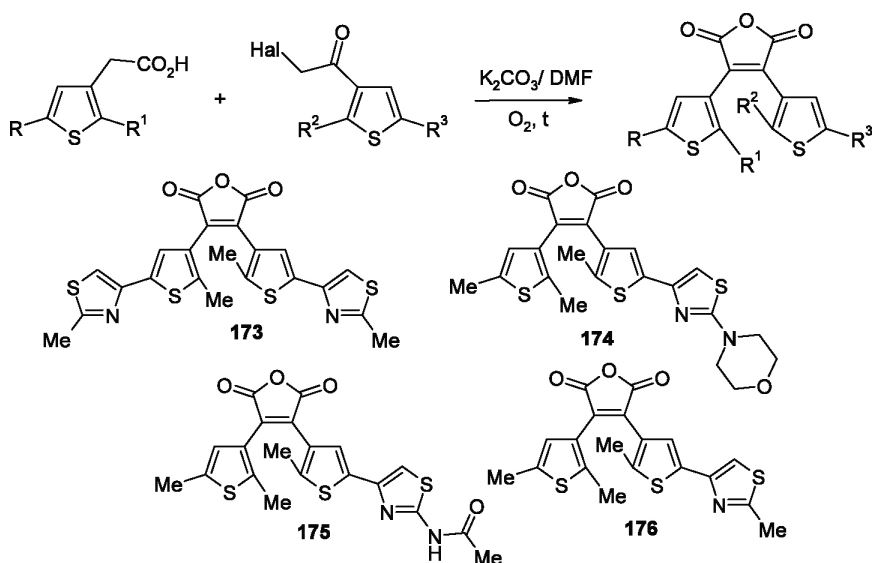
Scheme 53
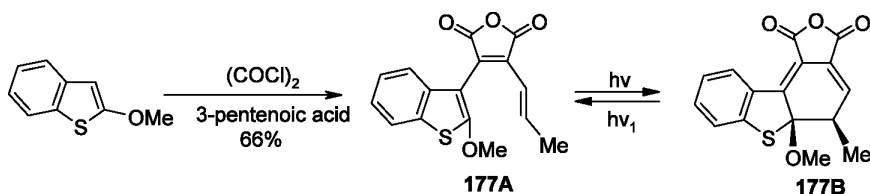
Scheme 54
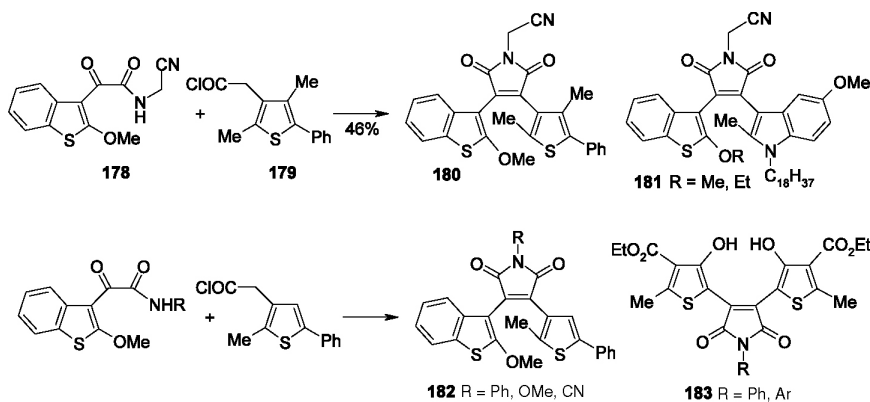
Scheme 55

afforded 3-[*N*-(cyanomethyl)oxamoyl]-2-methoxybenzothiophene **178**. In turn, 2,4-dimethyl-5-phenylthiophene was transformed into acid chloride **179** in a total yield of less than 5%, and the latter with the above-mentioned nitrile gave the target photochromic product **180**.

Diarylmaleimides containing optically active L- or D-menthyl groups at position 2 of the benzo[*b*]thiophene moiety (97JA6066) and unsymmetrical diarylmaleimides containing the benzothiophene and indole (05BCJ1145) or thiophene rings (04CL1398) (**181** and **182**, respectively) were synthesized according to a similar scheme. Derivatives **182** containing the methoxy, phenyl (04CL1398), or *o*-hydroxyphenyl (05CC3921) groups at the nitrogen atom, as well as di(2-thienyl)-substituted compounds **183** (06BCJ889), do not exhibit photochromic properties in polar solvents.

The conventional and efficient method for the synthesis of dithienylmaleimide **185**, according Scheme 56, was described by Chinese researchers (06TL9227). 2,3-Bis(5-bromo-2-methylthiophen-3-yl)fumaronitrile **184** was hydrolyzed with sodium methoxide–methanol followed by *N*-methylation with potassium *tert*-butoxide and iodomethane to give the target compound 2,3-bis(5-bromo-2-methylthiophen-3-yl)-*N*-methylmaleimide. Subsequent modification of the latter afforded **186** containing two ferrocene fragments.
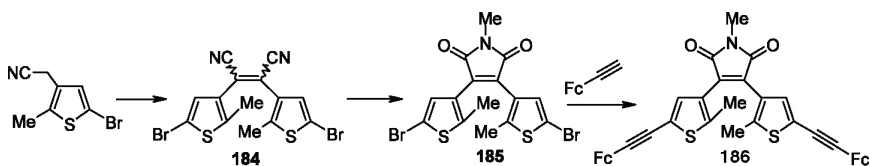
Scheme 56

Maleic anhydride derivatives are readily making it possible to perform their transformations into photochromic *N*-alkyl-substituted dithienylmaleimides with primary amines. This method was used to prepare cyclic imides **187** in anhydrous methanol or ethanol at 20–80°C in 67–90% yields (02ZOR1390) and *N*-alkyl(aryl) derivatives **188** based on thieno[3,2-*b*]pyrrole (03IZV1719) in 70–90% yields.
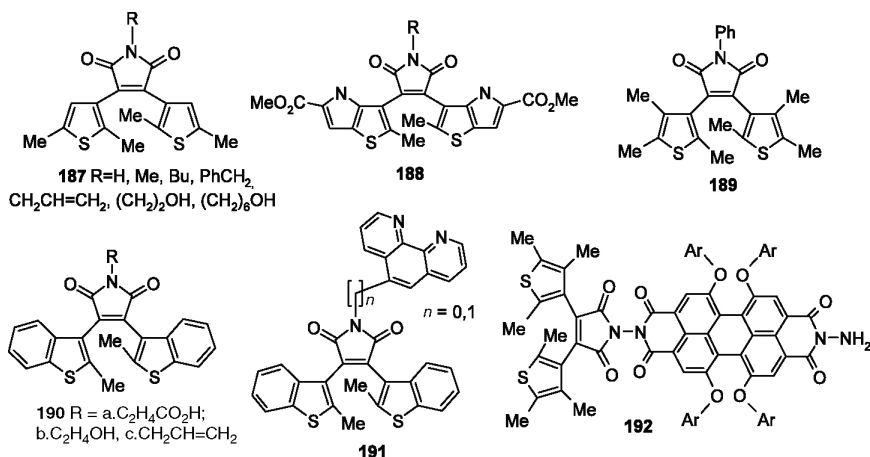
Aniline virtually quantitatively reacts with the corresponding anhydride in refluxing toluene in the presence of triethanolamine to form *N*-phenylmaleimide **189**, whose oxidation with *m*-CPBA affords unsymmetrical sulfone in 67% yield (08CC3281). N-Substituted compounds were synthesized in a similar way starting from (2-methylbenzo[*b*]thiophen-3-yl)maleic anhydride and *β*-alanine **190a** or 5-amino-1,10-phenanthroline **191** (the reaction was carried out under solvent-free conditions at 150 and 190°C, respectively) (08JA7286). Dithienylmaleimides **190b,c** containing the hydroxyethyl and allyl groups were introduced into silicon polymers, such as polysiloxanes and polysilazanes. They form transparent photochromic polymer coatings on silicate glasses under atmospheric moisture (08ARK112, 09VS1).

The synthesis of the bisthienylethene-functionalized perylene diimide **192** was accomplished in one step by the condensation of photochromic

2,3-bis(2,3,5-trimethyl-3-thienyl)maleic anhydride with a stoichiometric amount of the corresponding N,N′-diamido-1,6,7,12-tetra(4-*tert*-butylphenoxy)perylene-3,4,9,10-tetracarboxylic acid bisimide in refluxing toluene in the presence of imidazole catalyst (10LNG 6702).

In some cases, the formation of photochromic maleimides requires drastic conditions. Thus, hybrid *meta* and *para* derivatives **194** containing both fulgimide and diarylethene photochromic fragments were prepared in 61 and 75%, respectively, by refluxing amines **193** with anhydride **165** in ethanol under argon for 70 h in the presence of molecular sieves (06MI1, 11EJO) (Scheme 57).

However, the synthesis of *meta* and *para* derivatives **195**, as well as **197**, from fulgimide **196** requires even more drastic conditions. The reaction occurred only at high pressure (10 kbar); the yield of *para*-substituted photochrome **195** was 57%; the yield of the *meta* isomer was 34%; the yield of hybrid **197** was 11%. Hybrid product **199**, in which the photochromic fragments are directly linked to each other by an N–N bond, was synthesized similarly (06MI1) from fulgimide **198** (Scheme 58).

An alternative approach to symmetrical N-substituted maleimides (06ZOR1504) is based on the cross-coupling of boronic acid with 3,4-dibromobutylmaleimide giving imide **200** in 76% yield under reflux in dioxane in the presence of Pd(Ph$_3$P)$_4$ and CsF. This method can also be used for the preparation of unsymmetrical 3,4-substitued maleimides **203** through monobromides **201** and **202** (06ZOR1504). This general modification can be extended to other heterocyclic and aromatic boronic acids. In particular, an original one-pot procedure was developed for symmetrical or unsymmetrical bis(heteroaryl)maleimides involving the Suzuki–Miyaura cross-coupling sequence based on 3,4-dihalo-1-
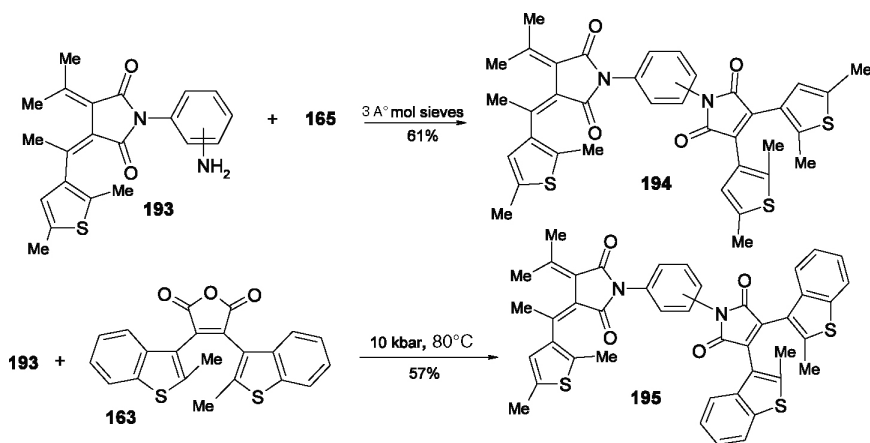
Scheme 57
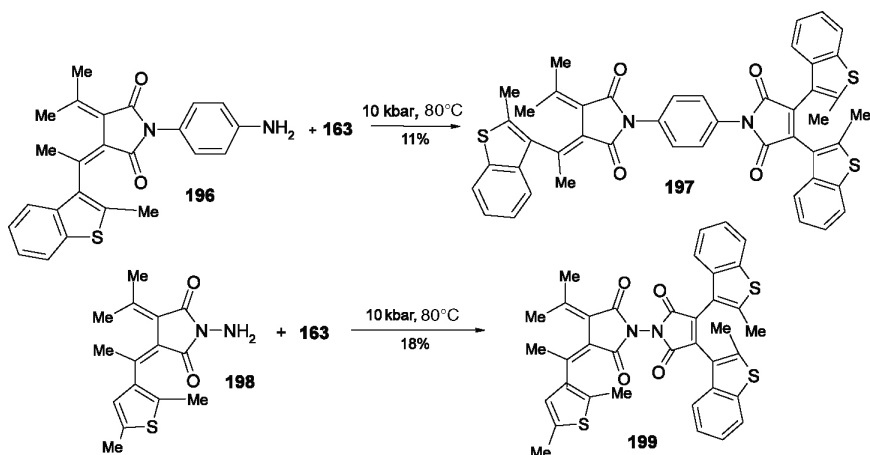
Scheme 58

benzyl-1*H*-pyrrole-2,5-dione with cyclic boronate esters **204** using PdCl$_2$(dppf) as the catalyst. The yields of **205** are 43–75% (O7T9482) (Scheme 59).

   Photochromes based on maleimides have now become relatively available. They can be hydrolyzed to the corresponding maleic anhydrides in 10% aqueous KOH with dioxane in a ratio of 3:1 (06MI1) (Scheme 60). The above-described approach to the synthesis of photochromes based on
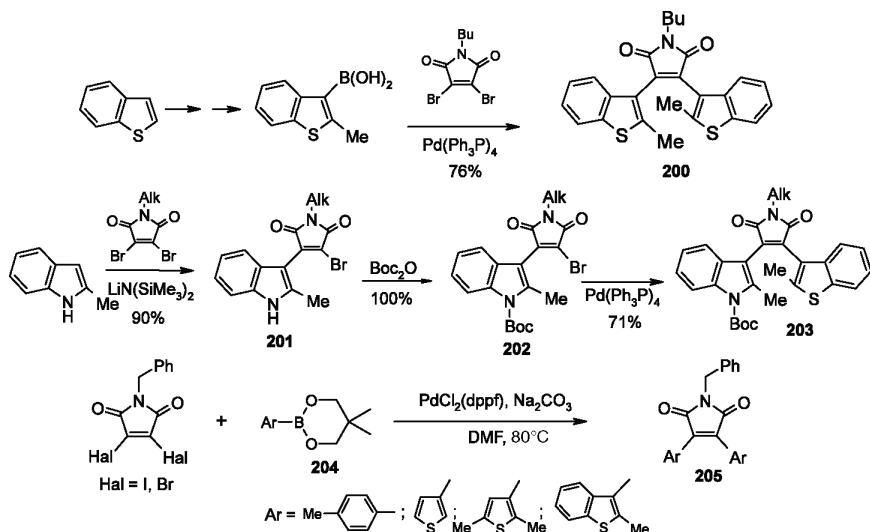
Scheme 59
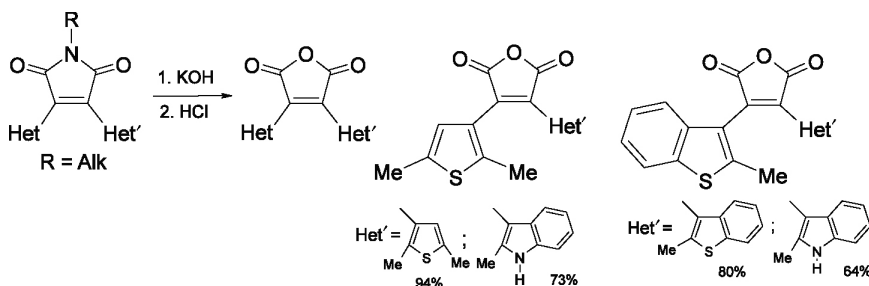
Scheme 60

maleic anhydrides from the corresponding maleimides is efficient taking into account their much easier preparation.

The following data are closely related to the results of a Russian team, who synthesized lactone- and lactam-bridged photochromes and studied their transformations. 2,5-Dimethyl-3-thienylacetic acid with α-chloro ketone in base gives ester **206**, which undergoes cyclization when heated with K_2CO_3 in DMF under an inert atmosphere to give lactone **207** in 70–75% yields (Scheme 61). The reaction can be performed *in situ* without isolation of the ester (06ZOR1827)

The condensation of **207** with dimethylformamide dimethylacetal affords dimethylaminomethylenefuranone **208** in high yield and
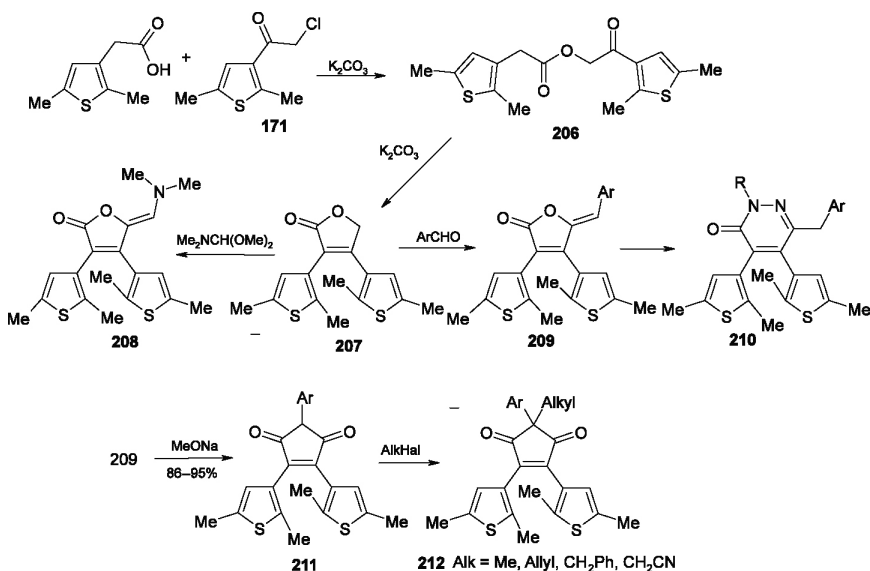
Scheme 61

methylene-active furanone **207** readily reacts with aromatic aldehydes when heated in ethanol with piperidine catalyst to form arylmethylene-furanones **209** in 70–85% yields. The latter with hydrazines gives dihetaryl-substituted pyridazinones **210** (08IZV2128) smoothly and affords products in high yields (80–95%). Hence, this approach serves as a convenient method for the synthesis of pyridazinone-bridged photochromes.

With sodium methoxide, arylidene derivatives **209** undergo a rearrangement into photochromic dihetaryl-substituted cyclopentenediones **211**. They are easily alkylated to form geminally substituted products **212** in 91–94% yields (07MC301). Their photochemical properties were investigated (07OS975, 08IZV853).

6. DTES WITH OTHER HETEROCYCLIC BRIDGES BASED ON THENOINES AND RELATED STRUCTURES

Considerable attention has been given to the construction of heterocyclic bridges of dihetarylethenes based on ethane-1,2-dione, 2-hydroxyethan-1-one, and 2-chloroethan-1-one derivatives. In many cases, readily available 2,5-dimethylthiophene is used as the starting compound. 2-Hydroxy-1,2-bis(2,5-dimethyl-3-thienyl)ethan-1-one **213**, one of the key substrates, was synthesized according to Scheme 62 (01IZV113).

Symmetrical and unsymmetrical thenoines **214–217** were synthesized analogously (02MI1). Thenoine 213 is easily transformed into 1,2-dione **218** and chloro ketone **219** (01IZV113). Ethane-1,2-dione derivatives **220** can be prepared by a one-pot reaction of 3-methylbenzothiophene with oxalyl chloride and AlCl$_3$ (02MI1) (Scheme 63).

The synthesis of unsymmetrical diketones **221–224** (05ZOR1375) and hydroxy ketone **225** (05ZOR895) containing indole substituents was documented (Scheme 64).
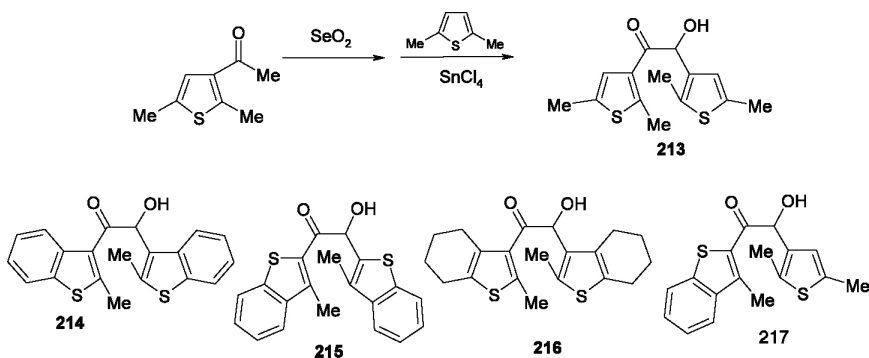
Scheme 62
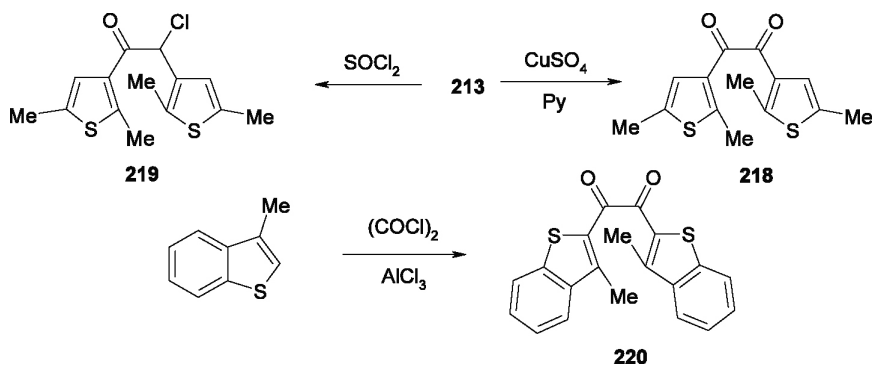
Scheme 63
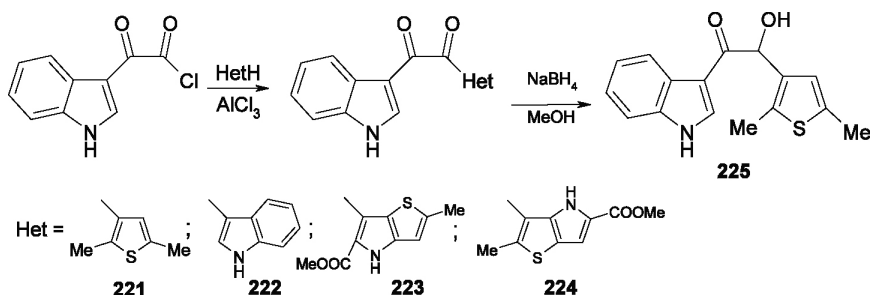
Scheme 64

Symmetrical and unsymmetrical thenoines, diketones, and chloro ketones **213–225** containing substituted thienyl, benzothiophene, and other moieties are versatile precursors of structures containing various heterocycles as bridges. Chloro ketones were used, for example, in the synthesis of photochromic thiazoles **226** (01IZV113) and tetrathiafulvalenes **227** (99CL1071) (Scheme 65).

More recently, a new method was developed (05MI3) for photochromic 4,5-dithienyl(dibenzothienyl)-1,3-dithiol-2-ones **229** and dithiol-2-thiones **230** from acetylene derivative **228** (Scheme 66). Compounds **230** are good building blocks for the design of photochromic fluorophores.

Evidently, the synthesis of fluorescent photochrome **232** (Scheme 67) occurs through the formation of a keto bromide from ketone **231** (08OL1319). The reaction of thenoine and its brominated analog with tetraol gives dimer **233**, although in very low yields (07JPOC960) (Scheme 67).

Scheme 68 presents simple and convenient approaches to the synthesis of photochromic diazines **234** (02MI1), oxazoles **235** (01IZV113),
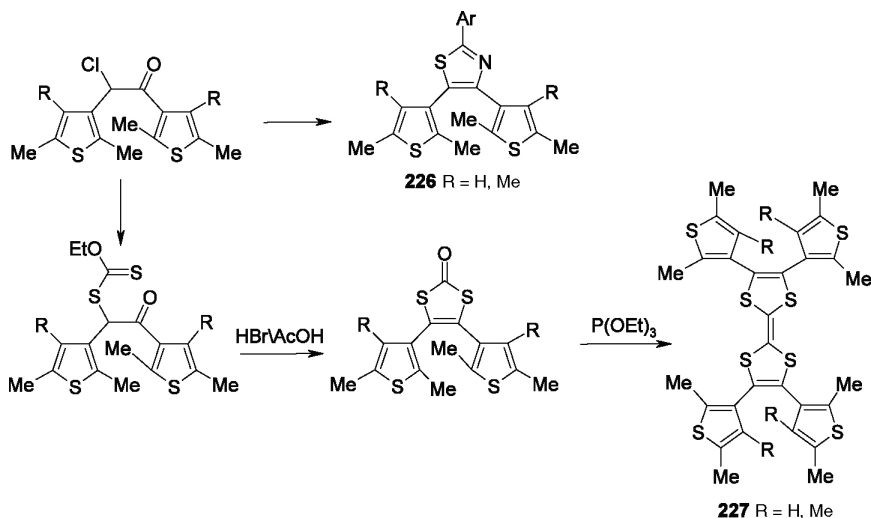
Scheme 65
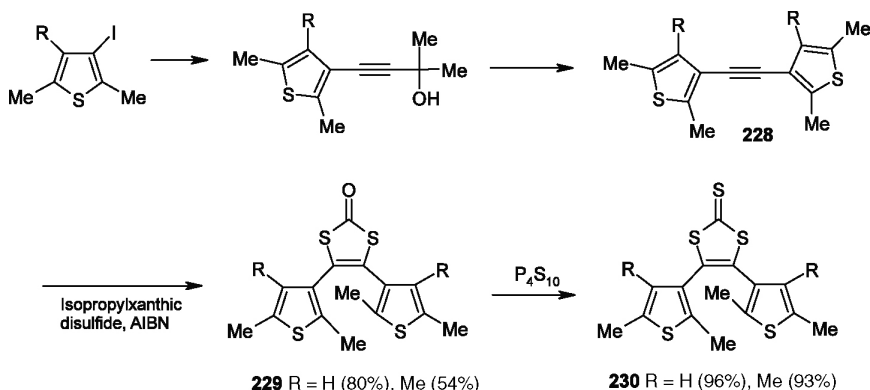
Scheme 66

tetrahydroindoles **236** (02MI1), as well as furans **237** and **238** (01IZV2315), starting from the readily available thenoine **213**.

Thenoines with urea in acetic acid give 4,5-bis(2,5-dimethyl-3-thienyl)-1*H*,3*H*-imidazol-2-one **239**, whose treatment with acid chlorides affords photochromes **240** in good yields (02IZV1588). Thenoine **213** with an excess of 1,1′-carbonyldiimidazole produces 1,3-dioxol-2-ones **241** in high yields (02IZV1588). However, thenoine with 1,1′-thiocarbonyldiimidazole gives 4,5-bis (2,5-dimethyl-3-thienyl)-1,3-oxathiol-2-one **242** instead of the expected thione (04ZOR1743) (Scheme 69).
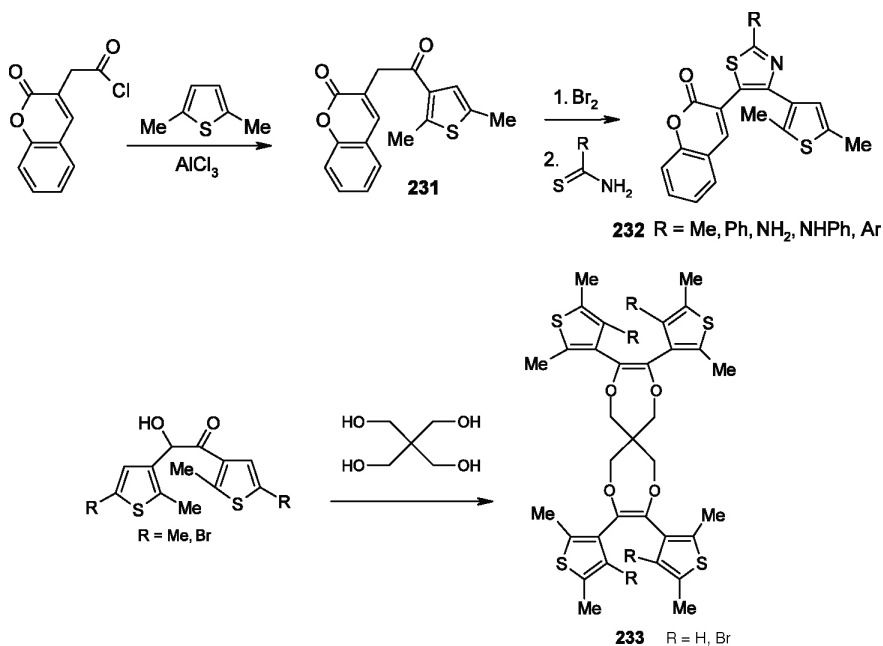
Scheme 67
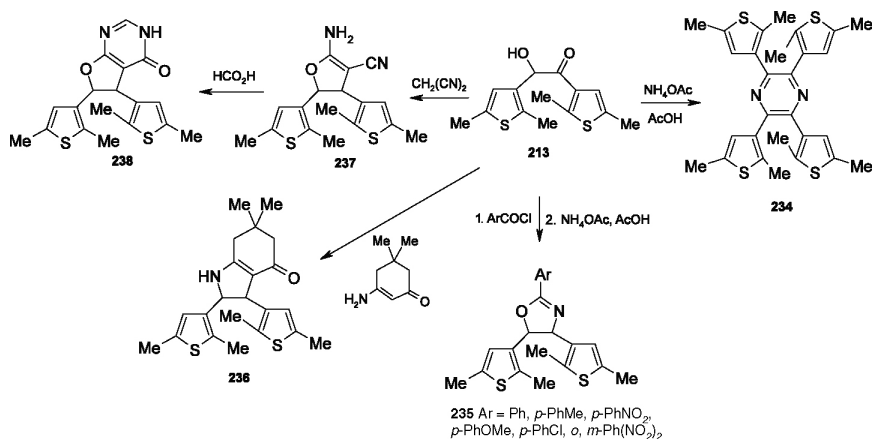
Scheme 68

The 1,3-dioxol-2-one ring in these compounds is relatively stable, thereby allowing acetylation, reduction, and the replacement of the keto group by a thione group giving photochromes **243–245** (02IZV1588, 05IZV1299).
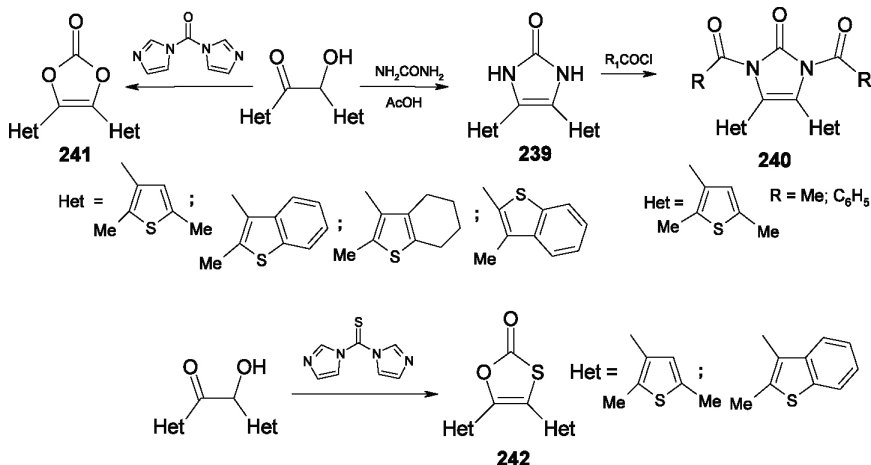
Scheme 69
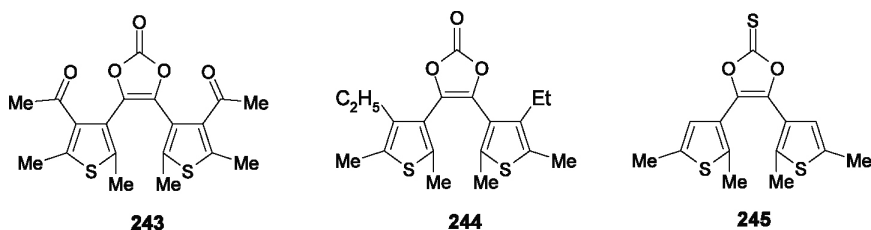
This same ring can be subjected to transformations to prepare photo-chromes **246** and **247** containing the oxazolidinone ring (02IZV1588, 05IZV1299) (Scheme 70), as well as to the synthesis of products **248** and **249**, in which the bridge is additionally bound to one of the two thiophene rings. Interestingly, product **248** containing a more extended conjugated system does not exhibit photochromic properties, unlike reduced **249** (04ZOR88).

The study (05ZOR89) showed that thenoines actively react with thiols in acidic media at room temperature to give β-keto sulfides **250** in good yields. On alkaline hydrolysis, the latter compounds are readily cleaved to ketones **251**, which are valuable intermediates for subsequent syntheses. In 06MI2, they were involved in a Fischer reaction and indole-"bridged" dithienylethenes **252** and **253** were obtained. Hence, a convenient procedure was developed for the transformation of readily available acyloins into photochromic indole-bridged dithienylethenes (Scheme 71).

R = H; Me;CH₂CH₂OCH₃; CH₂C₆H₅ ; CH₂C₆H₄CH₃-4 ;
CH₂C₆H₄Cl-4; CH₂C₆H₃Cl₂-3,4; CH₂C(O)C₆H₅
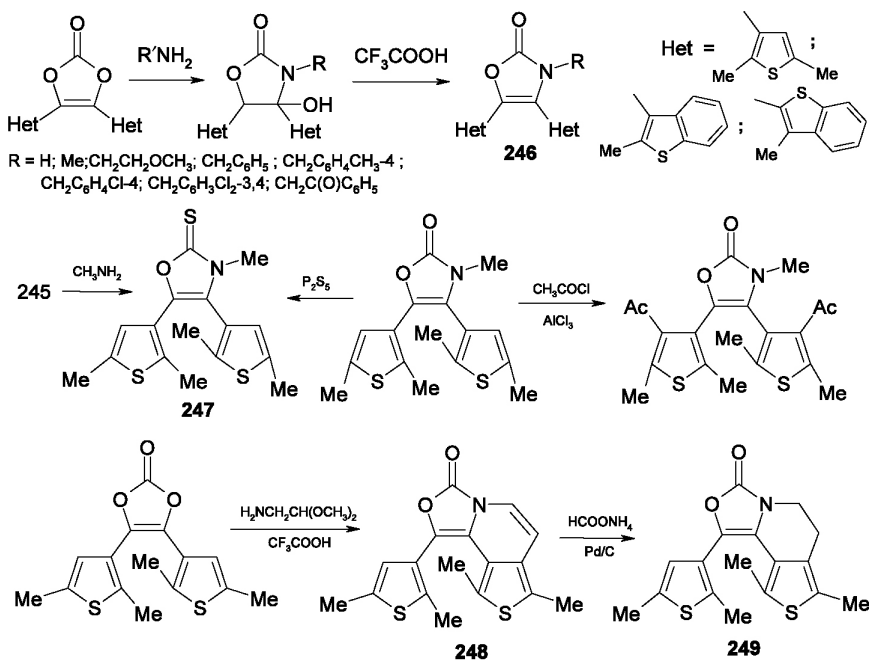
Scheme 70

Acyloin **213** with thioamides, thiosemicarbazides, and methyl dithio-carbazate in trifluoroacetic acid give photochromic thiazole-, thiadiazine-, and pyrazole-bridged dihetarylethenes **254**, **255**, and **256–258**, respectively (Scheme 72) (01IZV113, 06ZOR882).

In 06MI2, aminothiazole **259** was synthesized. Recently, Japanese researchers have used this method for the synthesis of benzothiophene analogs **260** and **261** (09NJC1368).
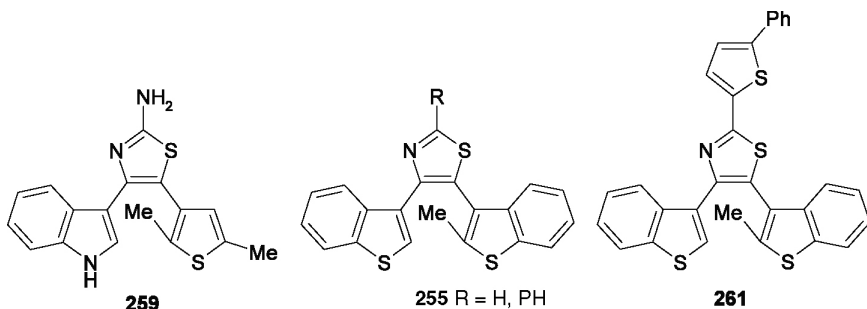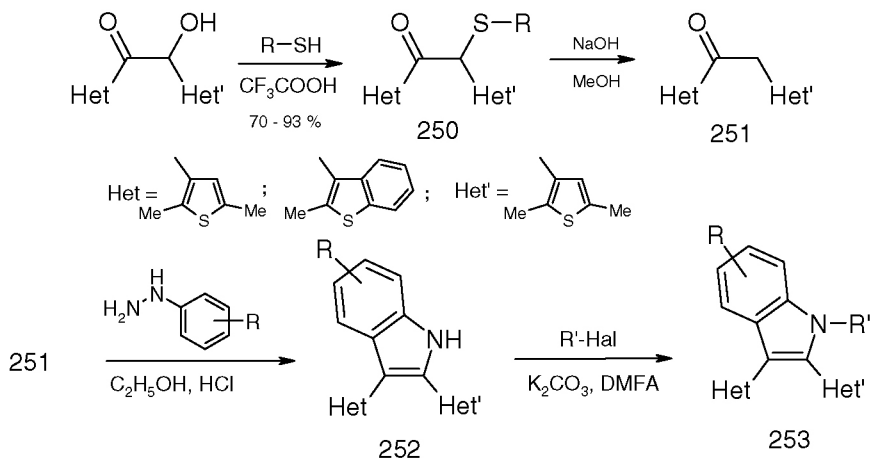
Scheme 71
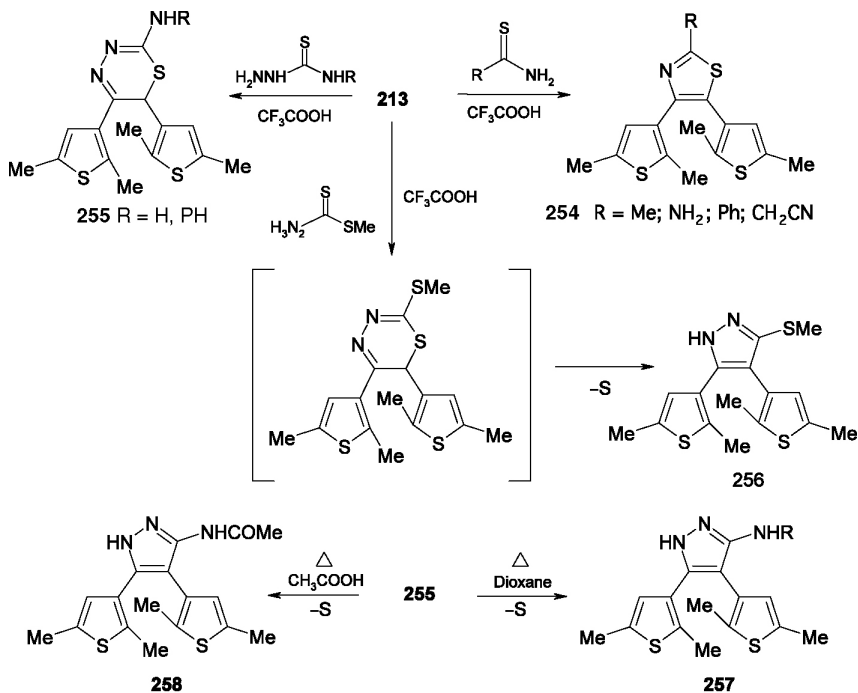
Scheme 72
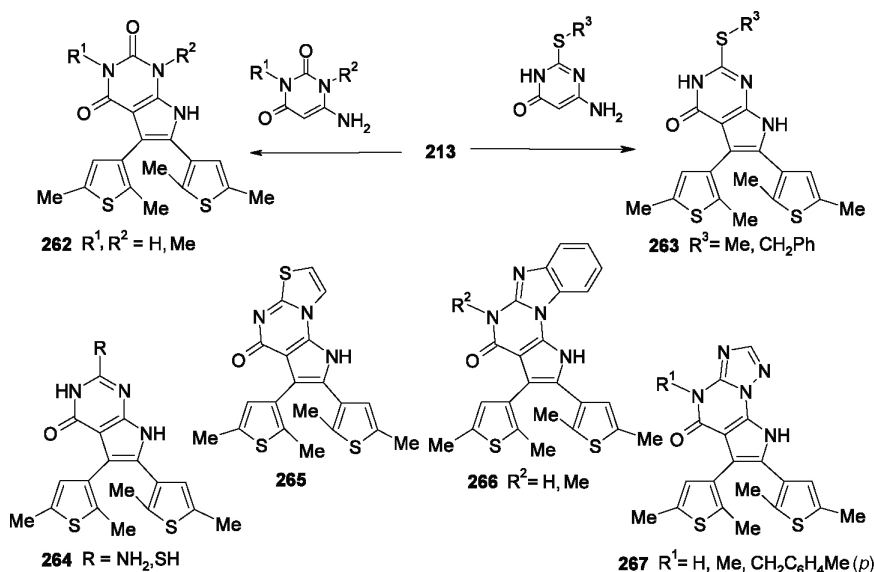
Scheme 73

Photochromic pyrrolo[2,3-*d*]pyrimidines **262–267** were prepared in 40–80% yields from thenoine **213** with substituted aminopyrimidines on heating in formic acid for 1–2 h (06MI2) (Scheme 73).

The nature of aromatic enamines has no substantial effect on the pathway; thus, pyrrolo[2,3-*d*]pyrimidines **265–267** were synthesized in comparable yields under the same conditions using thenoine **213** with fused aminopyrimidines (06MI2). Also new pyrrolo[2,3-*d*]pyridazines were prepared by the condensation of thenoine **213** with substituted 5-aminopyridazines **268** in formic acid followed by alkylation. Spectroscopic studies of **269** and **270** (Scheme 74) were reported.
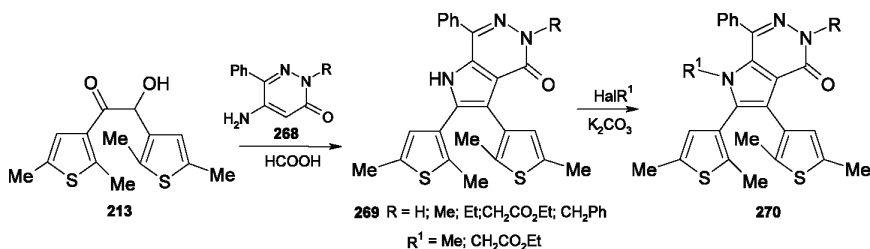
Scheme 74
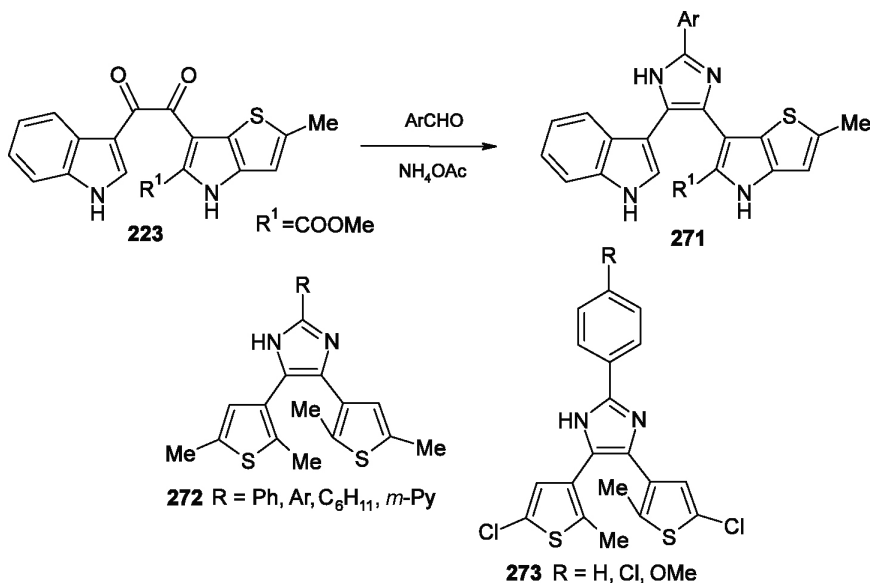
Scheme 75

The above diketones are also convenient and versatile starting compounds for the synthesis of photochromes containing heterocyclic bridges. Thus, ethane-1,2-dione **223** with aldehydes and ammonium acetate in acetic acid gave imidazoles **271** (Scheme 75) (05ZOR1375).

Diketone **218** with aromatic aldehydes and ammonium acetate afford the corresponding imidazoles **272** containing alkyl, pyridyl, or aryl groups bearing both electron-donating and electron-withdrawing substituents (01IZV113). Recently, imidazole-bridged 5,5′-chlorine-substituted dithienylethenes **273** have been described (09JPC(A)5550).

A series of substituted bis(2,5-dimethyl-3-thienyl)-1,2,4-triazines **274–276** were synthesized based on diketone **218** (01KGS89).
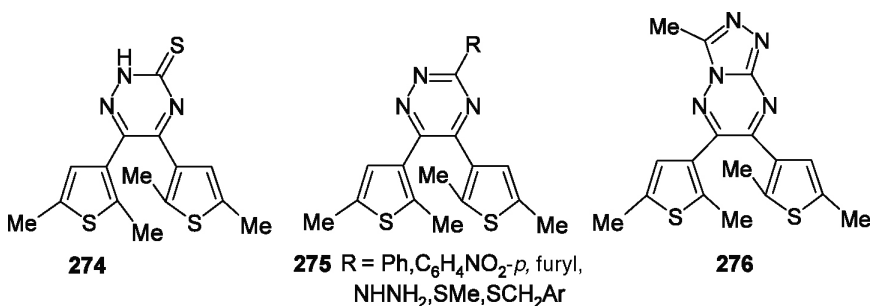
7. CONCLUSION

It is quite evident that the unique photochromic thermally irreversible dihetarylethenes hold great promise for practical application. The use in practice requires the synthesis of products with various physicochemical properties. To solve this problem, different approaches will be taken. Future investigations will necessarily include the search for new bridging fragments, the development of convenient methods for the synthesis of fused heterocycles, and the elaboration of approaches to the assembly of these components to form photochromic systems. Undoubtedly, these seemingly special problems of the chemistry of dihetarylethenes will stimulate the development of methods for the heterocyclic synthesis because the final goal, that is, the design of commercially available thermally irreversible photochromes, holds immense promise.

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10PJA472	M. Irie, *Proc. Jpn. Acad., Ser. B Phys. Biol. Sci.*, **86**, 472 (2010).
10RUP2378273	Ru. Patent 2378273 (2010).
11EJO	S.V. Shorunov, S.I. Luyksaar, I.P. Sedishev, M.M. Krayushkin, V.A. Barachevsky, and M. Irie, Eur. J. Org. Chem., (2011) (in press).

The Chemistry of Pyrido[1,2-*a*] azepines and Their Hydro Derivatives

Gunther Fischer

Contents

1. INTRODUCTION

1.1 General survey

In the field of *o*-fused, nitrogen-bridgehead compounds, fused 5/5, 5/6, and 6/6 ring systems (*pyrrolizines*, *indolizines*, and *quinolizines*, respectively) constitute large groups. Additionally, derivatives of the 6/7 ring assembly *pyrido[1,2-a]azepine* (**1**, Scheme 1), sometimes named *homoquino-lizine*, have proven to be of growing importance. Partially hydrogenated compounds and perhydrogenated *1-azabicyclo[5.4.0]undecane* (**2**) form frameworks of natural and synthetic substances having physiological activity.

While perhydro base **2** has been known since 1950, the potentially antiaromatic parent system **1** was, during the following decades, the target of much synthetic effort. Some early work comprising only a few substances had been included in an extensive review of nitrogen-bridgehead structures by Mosby (61HC(15)1247). Several pyrido[1,2-*a*]azepines showing maximum or nearly maximum unsaturation were later mentioned in Rodd's compilations (78RCC2(IVH)259, 87SRC(IVH)33, 98SSR (IVGH)147) and Katritzky's *Comprehensive Heterocyclic Chemistry* (96CHEC2(9)1, p. 25).
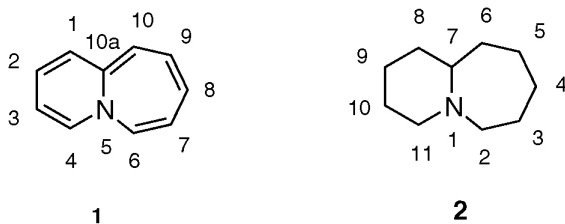
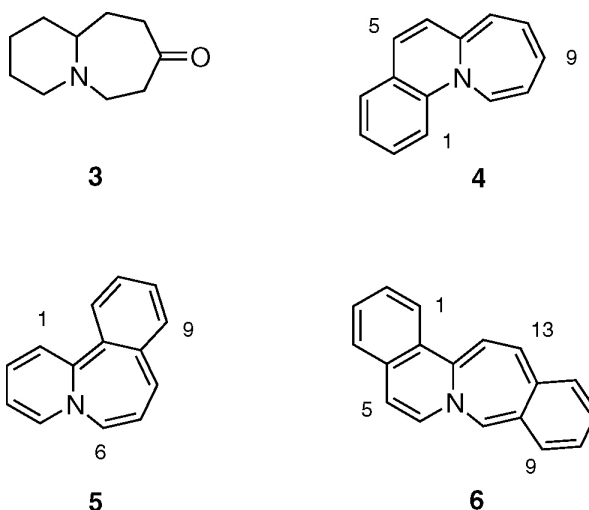**Scheme 1**

1.2 Scope and limitation

This review is based on Mosby's book cited above and covers the literature through 2009 together with several articles published in 2010. It includes pyrido[1,2-*a*]azepines and their hydro products as well as linearly or angularly fused benzo and dibenzo derivatives. Patents are taken into account provided they reveal important aspects of synthesis or application.

1.3 Nomenclature

The unsaturated and saturated species are numbered differently from each other as in formulas **1** and **2**, respectively. For consistency, they are in this review generally drawn as shown in Scheme 1.

The nomenclature is not quite uniformly used in the literature. According to Chemical Abstracts, perhydro compound **2** is *decahydropyrido[1,2-a]azepine*, but its oxo derivative **3** (Scheme 2), for instance, is named *octahydropyrido[1,2-a]azepine-8(2H)-one*. Examples of benzo-fused parent systems frequently dealt with in the following sections can also be found in Scheme 2 (98MI2; cf. Section 2.9.1):

- **4**: azepino[1,2-*a*]quinoline
- **5**: pyrido[2,1-*a*][2]benzazepine
- **6**: isoquino[2,1-*b*][2]benzazepine

3

4

5

6

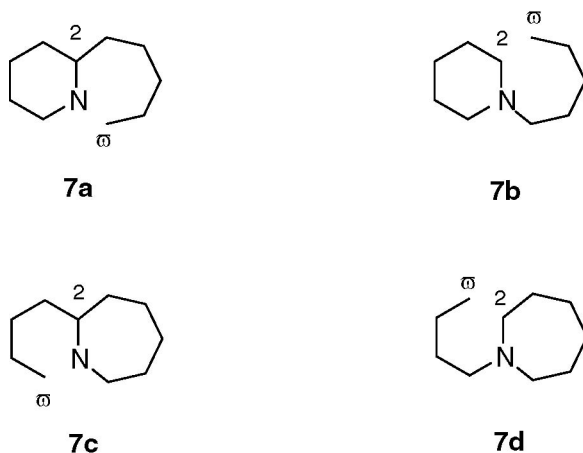**Scheme 2**

2. OCCURRENCE AND SYNTHESIS

2.1 Survey

After a short view of the natural occurrence (Section 2.2) the synthetic Sections 2.3–2.8 are arranged in the order of increasing unsaturation of the target compounds, beginning with perhydrogenated base **2** and ending in parent system **1**. Some concluding remarks form Section 2.9.

To avoid any confusion arising from the pyridoazepine nomenclature (see Section 1.3), the synthetic sections will be denoted according to the respective *unsubstituted* bicyclic parent moiety ("*derivatives* of decahydro-pyrido[1,2-*a*]azepine," etc.).

Preference will generally be given to the cyclization step; early precursors can often only be indicated. The further subdivision of the sections depends on the ring existing in the precursor (annulation onto the six- or seven-membered ring or transformation of other precursors). Instead of excessive subdividing reaction sequences reported in the literature, subsequent reactions of cyclized products will sometimes be included in the synthetic formula schemes of Section 2; they will later in due course be described in Section 4.

A majority of routes leading to bicyclic pyridoazepines schematically falls into four categories (Scheme 3): They can be described as 1.2$^{\omega}$ or 2.1$^{\omega}$ cyclizations, each of them basing on a pyridine (**7a** and **b**, respectively) or an azepine derivative (**7c** and **d**, respectively). Among the synthetic methods involved are classical ones (*N*-alkylation, lactamization, Dieckmann condensation, etc.) and an increasing part of enamine, enamide, and

Scheme 3

iminium ion reactions, including cycloaddition and ring transformation. Beginning in the 1990s, the transition-metal-catalyzed *ring-closing metathesis* (RCM) has become a valuable synthetic tool (see Sections 2.4.1.6, 2.4.2.4, 2.5.1.4, 2.5.3.2, 2.6.1.2, 2.6.2.1, 2.7.1.6).

2.2 Natural occurrence

Euphorbiaceae alkaloid astrocasine (**8**), together with its reduction products dihydroastrocasine (**9a**), desoxyastrocasine (**9b**), and dihydrodesoxyastrocasine (**9c**), is shown in Scheme 4. Its structure had been proposed on the base of spectral data and a partial degradation leading to carboxylic acid **10b** (65TL1761) and was confirmed by X-ray diffraction with its methobromide **353b** (see Scheme 80) (76JOC2454). A similar plant constituent, astrocasidine (**9d**), and a proposed biosynthetic pathway of the group were published (72AQ769).

Alkaloid saulatine (**11**, Scheme 5), which was isolated from Guayanese plant *Abuta bullata*, has the isoquino[1,2-*b*][3]benzazepine ring system (84JNP539). Moreover, the pyrido[1,2-*a*]azepine skeleton, additionally N- or O-bridged and/or heterocyclicly fused, has been found in a great number of plant substances, for instance, quinicarcin (**12**) (04EJO3611), *Stemona* alkaloids (08PAC751), and antibiotic lemonomycin (00TL2067).

2.3 Synthesis of decahydropyrido[1,2-a]azepine derivatives

### 2.3.1 By annulation onto the six-membered ring

2.3.1.1 *N*-Alkylation and lactamization

7a-Type precursors **13** and **16** (Scheme 6) through bromides give *β*-hydroxyamides **14a** and **17**, respectively (59AP143, 59CCC1846), the latter forming together with isomeric 4-hydroxymethylquinolizidine. Both the 1-azaundecanes finally yield parent substance **2** that can also be obtained from imines **18** or **59** (see Scheme 16). Lactam **19** results in poor yield from 6-(4,5-epoxypentyl)-2-piperidone (80JOC3664).

Products of the cyclization by thermal lactamization (**20** and **21**) are shown in Scheme 7 (59CCC2318, 62CPB366).

2.3.1.2 Dieckmann condensation (Scheme 8)

Aminoketones, such as **3** and **23a** and **b**, are prepared by the cyclization of the appropriate diesters using sodium hydride in boiling toluene or xylene at high dilution (92BML1147, 96BMC255). A modified method is that of cyclizing monoester-mononitriles to give aminoketones **15** and **23a** (71JHC7, 76JPS1389).
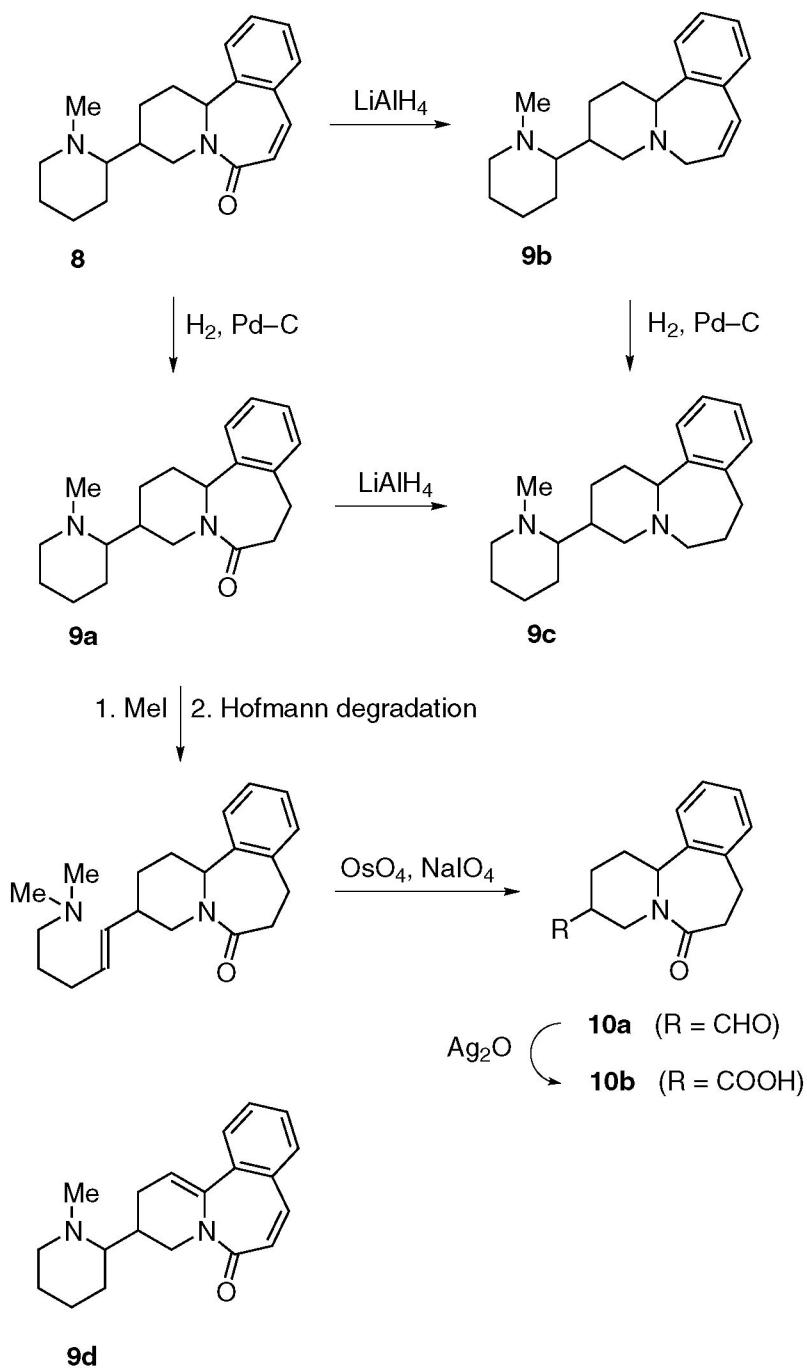
Scheme 4
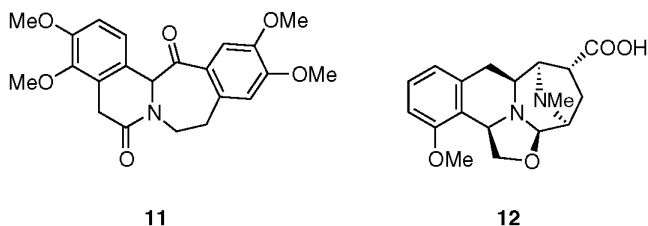
Scheme 5

2.3.1.3 Iminium ion cyclization (Scheme 9)

In the **7b**-type synthesis of peptidomimetic precursor **30a** (cf. Section 5.1), the keynote step involves *intramolecular N-acyliminium ion cyclization* of *N*-acyl enamine **27**, the attacking nucleophile in this case being an olefinic group. The original route leads from intermediate **27** through triflate **28** to a mixture of iodide **29a** and two regioisomeric elimination products **29b**; both **29a** and **b** were separately reduced to give chiral lactam **30a** (94TL393). A modified method (bold arrows) is superior as to convenience and yield (06SC965).

An example of a smooth *α-acyl iminium ion-acetylene cyclization* is that synthesizing ketolactam **31** via the *in situ* capture of the ion by the terminal acetylene group (80T143). The seven-membered ring could not be closed, however, on an existing six-membered ring iminium ion in the case of the tetrahydropyridinium isomer of salt **38b** (see Section 2.3.2.2) (79JOC4173). Just recently a gold-catalyzed synthesis of **23a**-type bicyclic ketones via a two-step [5 + 2] annulation has been described, performed by the alkylation of piperidines with *in situ* generated 5-iodopent-1-yne, *m*-chloroperbenzoic acid (CPBA) oxidation, and cyclization in the presence of gold catalysts (10CC3351) (cf. the synthesis of isomer **49**, see Scheme 14).

2.3.2 By annulation onto the seven-membered ring

2.3.2.1 Lactamization and *N*-alkylation

Bicyclic imide **32** (Scheme 10) was obtained from the **7c**-type precursor (64CB1542). Acyliminium ion addition products **33a** and **b**, when hydrogenated and afterwards cyclized, give diastereomers **34a** and **b** (01TL6995).

Another stereoselective synthesis (Scheme 11) is based on sugar aldehyde **35** and intermediate **36**; subsequent 1,2-*O*-isopropylidine deprotection, *N,O*-debenzylation/olefin reduction/reductive cyclization in a single pot, and *O*-acetylation result in the formation of bicyclic aza sugar **37** (09TA1217).
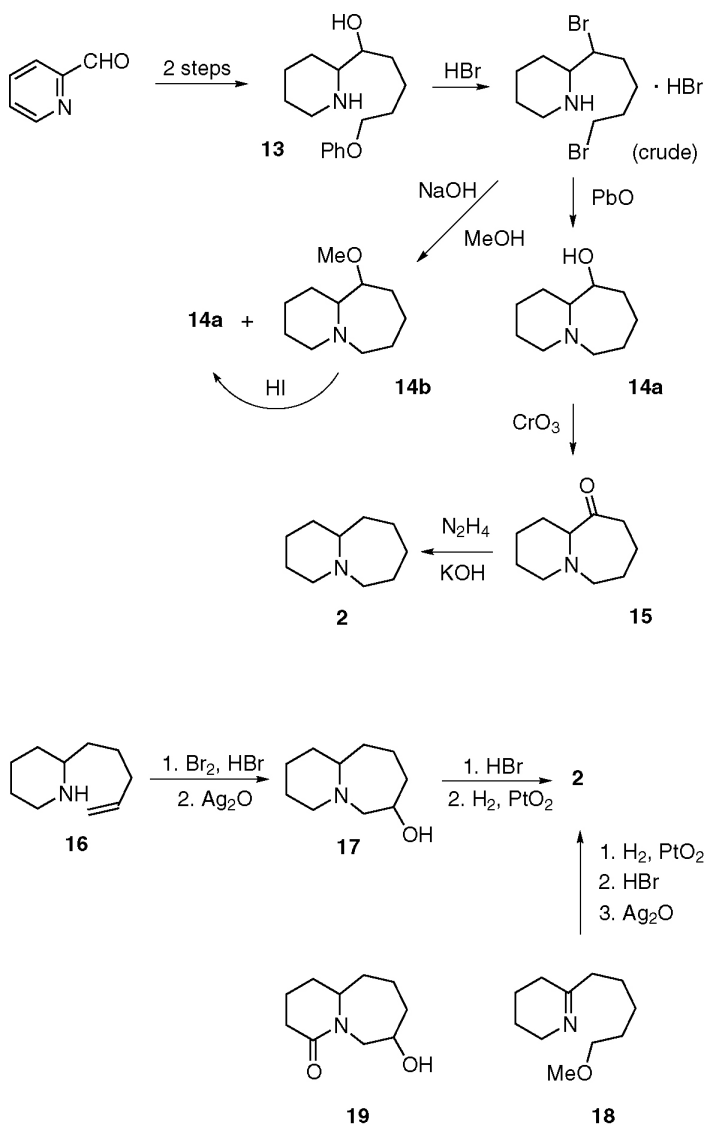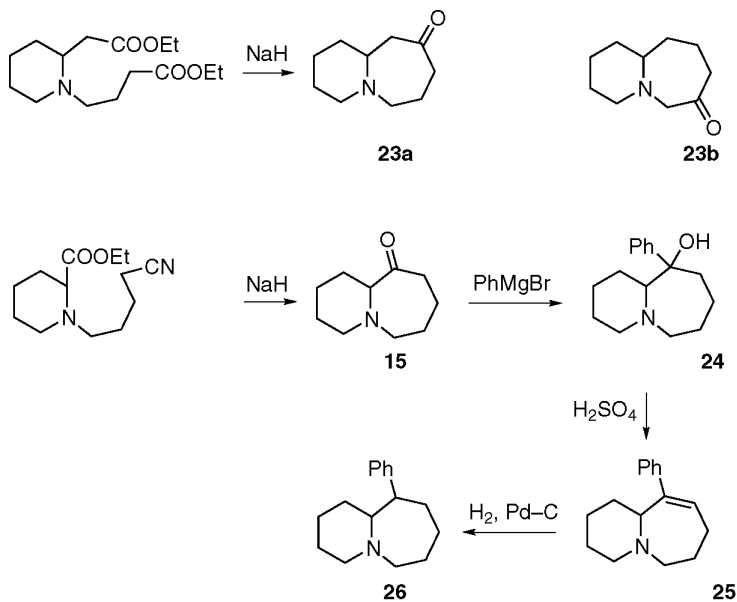
Scheme 6

2.3.2.2 Iminium ion cyclization (Scheme 12)

An example of the **7d**-type cyclization is that of iminium salt **38b** obtained by decarbonylation of α-(*tert*-amino) acid **38a**. Attack of the nucleophilic malonate on the newly formed electrophilic carbon of the iminium ion gives dicarboxylate **39a** (79JOC4173).
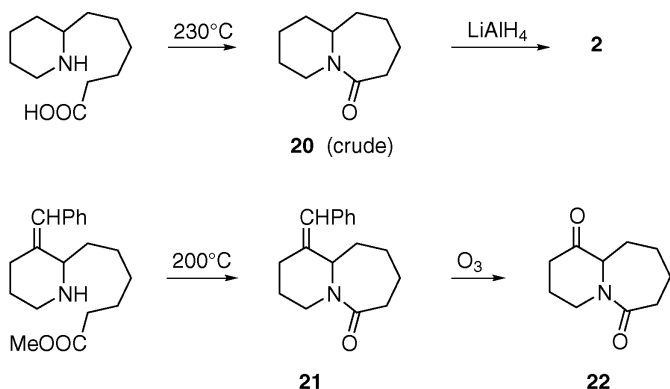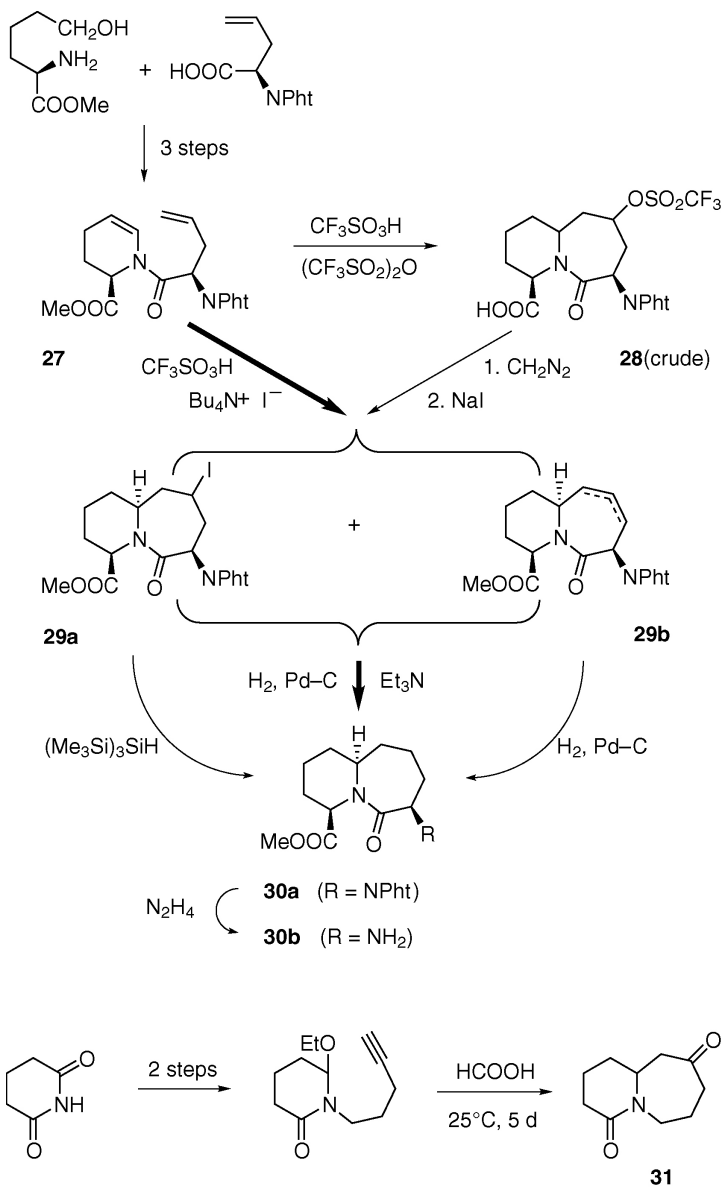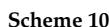
Scheme 7

Scheme 8

Organoaluminum-promoted Beckmann rearrangement/methylation of cyclohexanone oxime mesylate, followed by allylation of ketimine **40a** and Mannich cyclization of the intermediate iminium-allylsilane, provides piperidine **40b** possessing *exo*-unsaturation (08BKC1669).
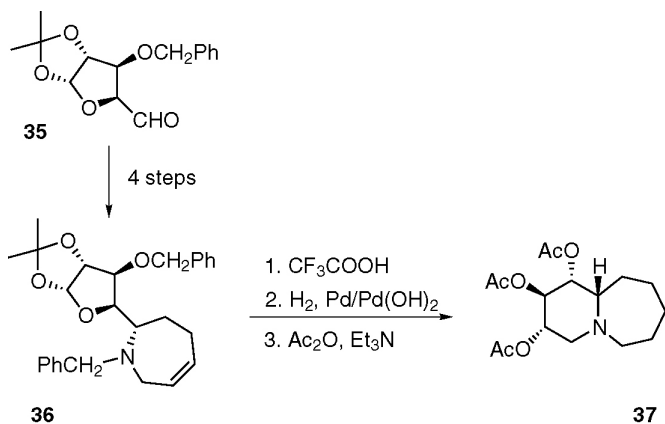
Scheme 9
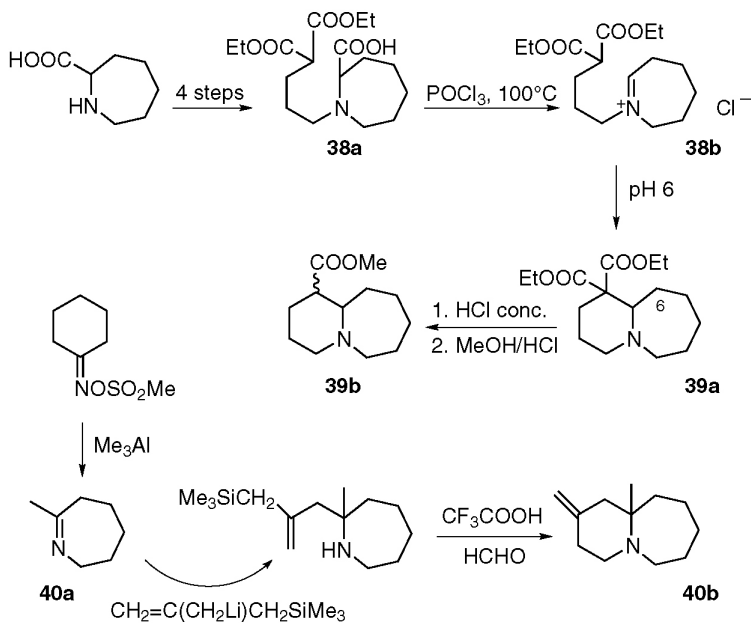
Scheme 10

2.3.2.3 Photocyclization (Scheme 13)

Irradiation of γ-ketoamide **41** affords stereoisomeric lactams **42a** and **b** via hydride abstraction from ε-position to the keto group (88H(27)133, 98T2529). The observed stereoselectivity in dichloromethane (88% **42a**) is significantly higher than that obtained in *tert*-butanol. An additional stereocenter in *β*-position to the keto group of amide **41** inverts the diastereoselectivity (98MI1).

2.3.2.4 Cycloaddition and cyclocondensation (Scheme 14)

A [3+3]-type annulation between α,α′-dimethoxylated lactam **43** and allyltrimethylsilane gives bicyclic lactam **44**. The reaction proceeds presumably through the allylation at the α-position followed by the intramolecular addition of the cation developed at the α′-position to the allylic double bond (85JOC3243). The aza-Diels–Alder reaction of

Scheme 11

Scheme 12

1-alkyliminium salt **45** and simple olefins affords cycloadducts (e.g., **46a** and **b**).[1] Their reduction results in small yields of the saturated bases (e.g., **47a** and **b**) (93SC253).

---

[1] In the captions beneath the formulas, substituents (R) in parentheses refer, in the order given, to substructures **a**, **b**, **c** etc. of the respective formula or all formulas of the reaction.

Scheme 13

Scheme 14
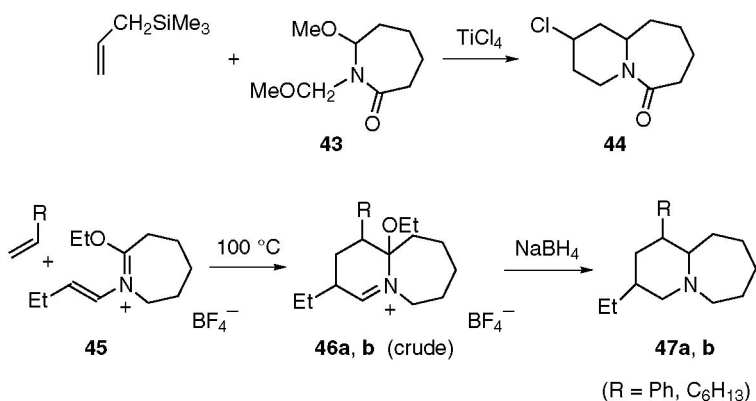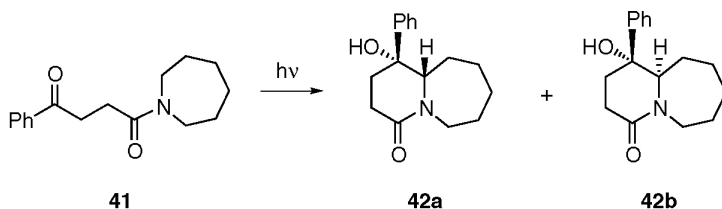
Tertiary *N*-butynylamine **48** when oxidized generates an *N*-oxide inter-mediate that is cyclized *in situ* via gold catalysis to give bicyclic piperidone **49** (09JA8394). As amine **48** can be prepared readily, the overall transfor-mation constitutes a formal [4+2] synthesis.

2.3.3 By other approaches

In the course of biogenesis-type syntheses of lupin alkaloids, reduction of protected macrocyclic acyloin **50** (Scheme 15) has been found to be a second route to bicyclic aminoalcohol **14a** (69JA7372). Another 11-membered ring compound, namely caprinolactam (**51**), on anodic oxida-tion in the presence of halide ions produces 6/7 bicyclic lactam **52** together with two isomeric 5/8 bicyclic lactams (87CJC2770).
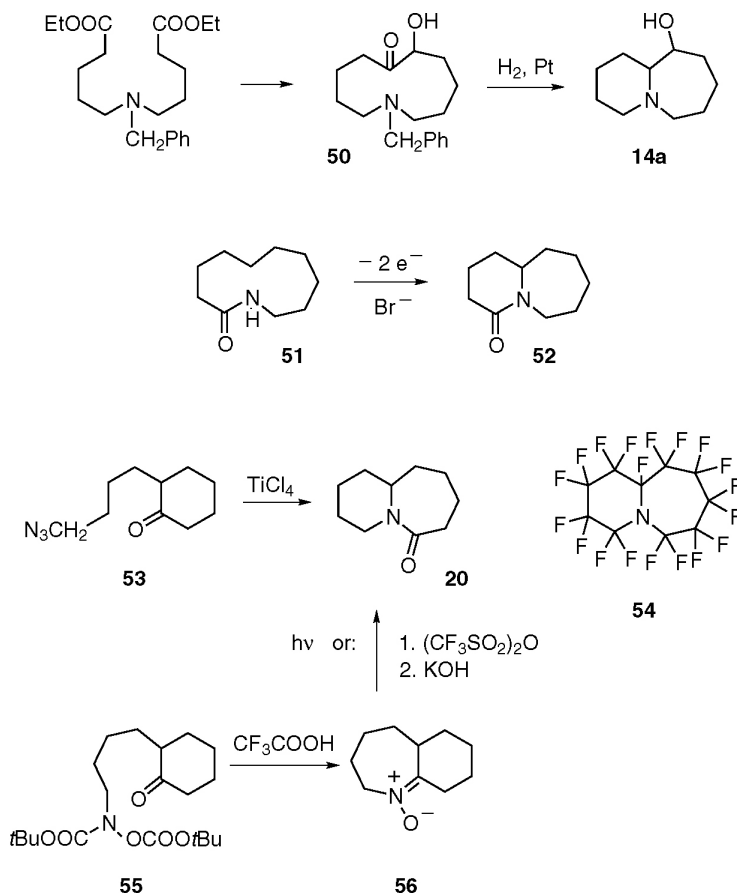
Scheme 15

An example of ring enlargement is the intramolecular Schmidt reaction of azidoalkyl ketone **53** that gives, by the action of titanium tetrachloride, through intermediate azidohydrin, lactam **20** (95JA10449). Because of the large distance between keto and azido groups, the usual catalyst trifluoroacetic acid does not work.

Electrochemical perfluorination of 4-methylquinolizidine gives rise to a small amount of by-product perfluoro-1-azabicyclo[5.4.0]undecane (**54**) (88JFC(38)303).

The transformation of endocyclic nitrone **56** (made from *N,O*-bis-protected hydroxylamine **55**) to lactam **20** can be carried out by photo-chemical activation or by a two-step modification of Barton's protocol, that is, by trapping the nitrone oxygen followed by an alkali-promoted, semi-pinacol-like rearrangement (03JOC8065).

Finally, 1-aza-bicyclo[5.4.0]undecanes are reduction products (see Section 4.3) of, for instance, *β,γ*-unsaturated amines **25** and **95b** (see Scheme 24), iminium salt **60** (see Scheme 16), and enamine **107** (see Scheme 27).

2.4 Syntheses of octahydropyrido[1,2-a]azepine derivatives

### 2.4.1 By annulation onto the six-membered ring

2.4.1.1 Alkylation and lactamization

Spiro-isoxazoline **57** (Scheme 16) undergoes thermolytic rearrangement followed immediately by cyclization of the intermediate enaminone to bicyclic **58** (89J(P1)1253). Imine **59** when heated gives iminium salt **60**, hence providing a new and efficient route to parent substance **2** (03T3099).

Silyl-protected azidoallene **61** (Scheme 17) is by the *endo*-mode ring closure converted to enaminosulfone **62a** that, after deprotection and bromination, in a second cyclization affords bicyclic **63** (04JOC2128). Allylacetate **64b** undergoes *endo*-cyclization (*intramolecular conjugate displacement*), when the nitrogen protecting group is removed, to yield bicyclic ester **65** (07JOC5608). In a similar way protected *α*-(pipecoloylethyl)
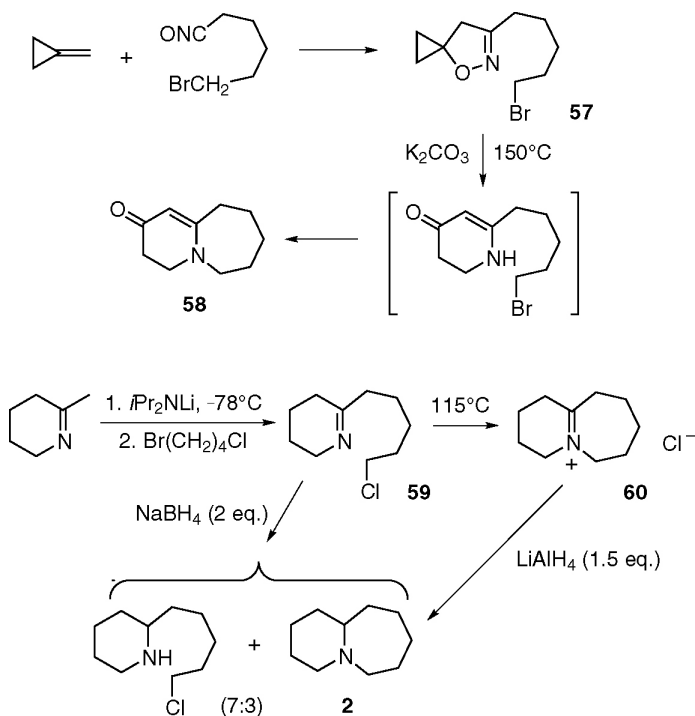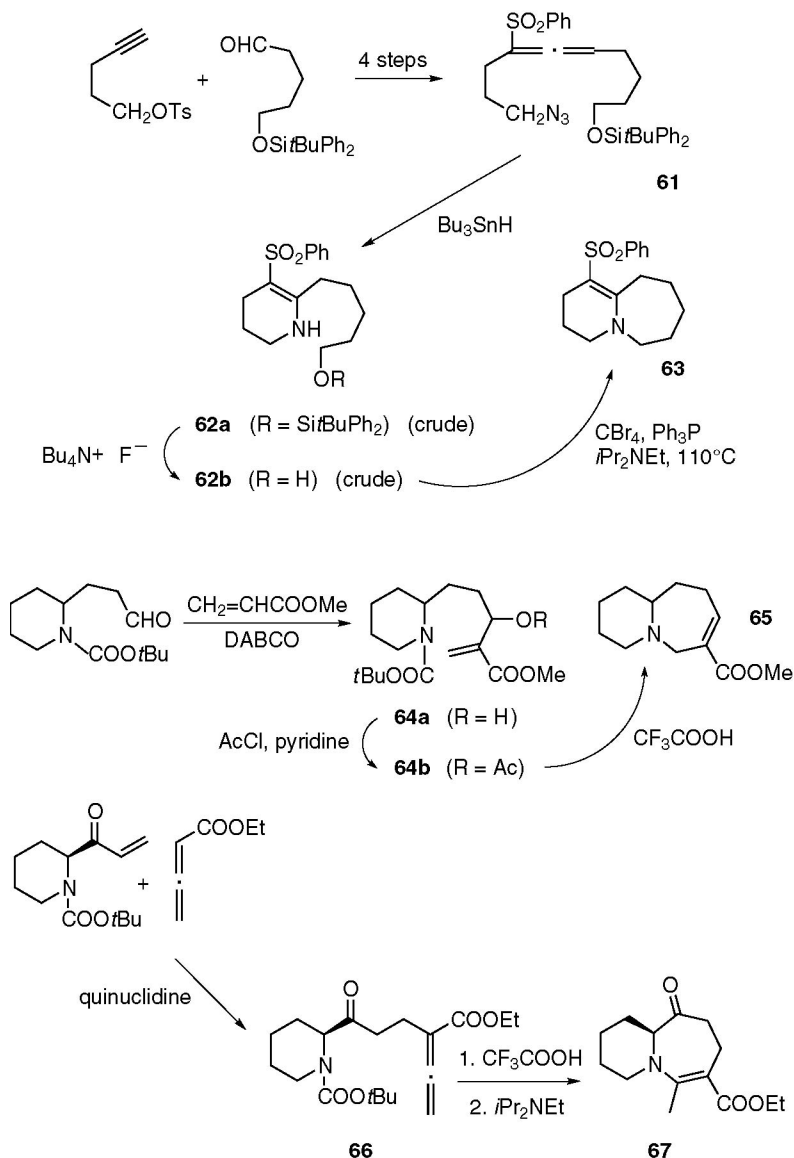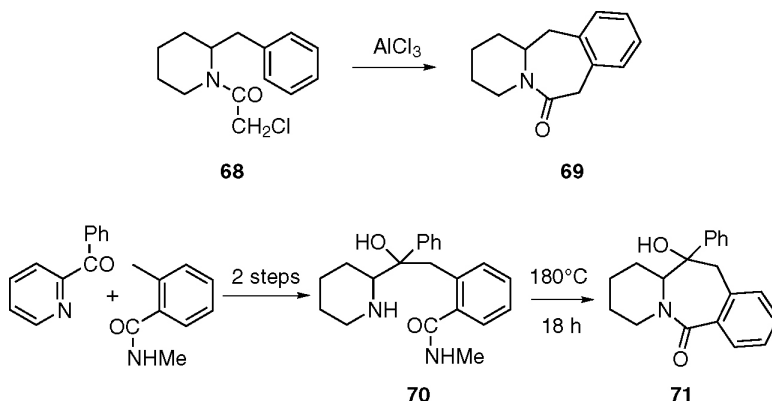

Scheme 16

Scheme 17

allenic ester **66** (obtained by amine-catalyzed *enone–allenoate coupling*) gives, in a one-pot deprotection and intramolecular 7-*endo-dig* cyclization in the presence of Hünig's base, chiral carboxylate **67** (05T6309).

Examples of benzo-fused derivatives (Scheme 18) are those of pyrido [2,1-*b*][3]benzazepine **69**, produced by the intramolecular Friedel–Crafts
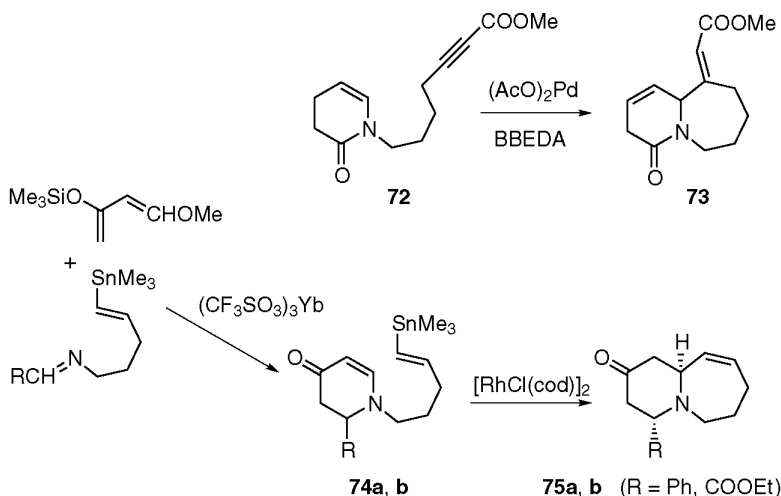
Scheme 18

alkylation of amide **68** (99WO32453), and pyrido[1,2-*b*][2]benzazepine **71**, which is the result of the intramolecular transamidation of amide **70** (74USP3824244).

### 2.4.1.2 Enamine and iminium ion cyclization (I)

Enamines (cf. 63JCE194, 82T1975, 88MI1, 08H(75)1849) play an important role in the syntheses under review, both as target substances (see Schemes 16 and 17) and as precursors (see Scheme 9 and following Schemes 19–21). Thus, noble-metal-catalyzed enyne and diene cyclizations have been described (Scheme 19): palladium-catalyzed cycloisomerization of

Scheme 19

N-alkinyldihydropyridone **72** yields bicyclic lactam **73** (92JA7292), and rhodium-complex-catalyzed *intramolecular conjugate addition* of vinylstannanes **74a** and **b** (formed by aza-Diels–Alder reaction) leads to chiral piperidones **75a** and **b** (08T3464).

Enamine carbaldehyde **76** (Scheme 20) by sequential photochemical cycloaddition and *iminium ion–propargylsilane cyclization* furnishes allenes **77a–c** in good yield and with high diastereoselectivity (92T2081). (Gas chromatographic t_R values and thin-layer chromatographic R_F values have been reported.) Radical cyclization of ω-iodoalkyl isoquinolone **78a** under
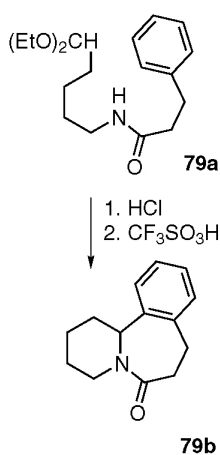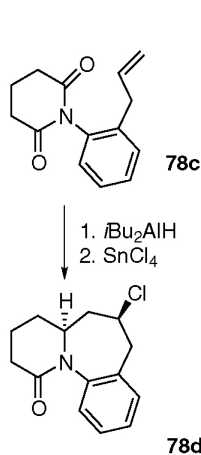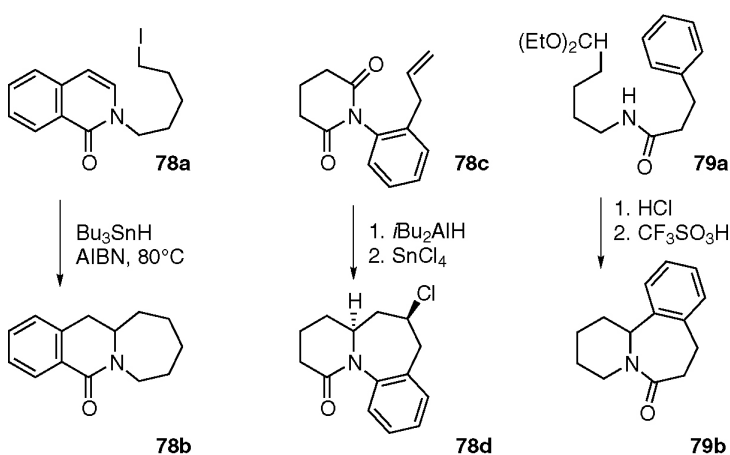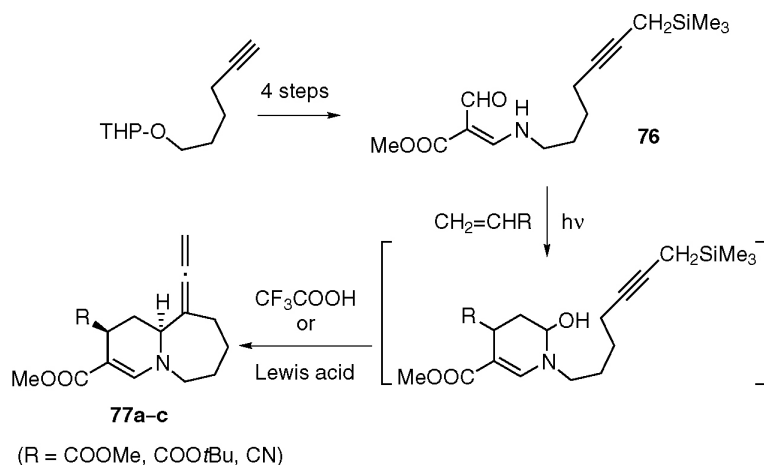
Scheme 20

tributylstannane-mediated reductive conditions affords tricyclic **78b** together with a reductively dehalogenated, uncyclized by-product (04TL2855).

The *N*-acyliminium ion cyclization of glutarimide **78c** with terminal alkene does not show the usual selectivity in favor of ring contraction; pyridobenzazepine **78d** and the isomeric chloromethylquinolizidine are isolated in nearly equal amounts (10OL1696).

2.4.1.3 Iminium ion cyclization (II) to yield pyrido[2,1-a][2]benzazepines

The formation of lactam **79b** from amide **79a** as recently published (09OBC3561) is placed first here; it proceeds in two steps via acetal hydrolysis and electrophilic cyclization of the intermediate piperidinium salt.

Flynn's group (87MI1) has aimed at the synthesis of conformationally restricted dipeptide mimics (e.g., **83**, Scheme 21) as inhibitors of *angiotensin-converting enzyme* (ACE; see Section 5.1); they have developed an acyliminium ion Friedel–Crafts type cyclization onto an unactivated phenyl ring. Since then the procedure has been elaborated for technical purpose. The crucial cyclization (one-pot reaction of **80** to give **81a**) can be divided into two steps (95WO14663). Alternatively the reesterification after the acid-catalyzed ring closure of enamino ester **80a** was accomplished by diazomethane to yield methyl ester **84b** (87EPP249223).

Acid **84a** (MDL 28726) has proven to be the key intermediate in the production of inhibitor **83**; effective syntheses including the precursors have been developed and optimized (99OPD241, 05WO110986, 08OPD940). A similar route leads to potential caspase activator **84c** (08JME7352).

2.4.1.4 Thermolysis and electrolysis (Scheme 22)

The synthesis of iminium salt **85** by soda-lime pyrolysis through an intermediate enamine (83CJC2016) is inferior to that of salt **60** (Scheme 16). Cathodic cyclization of 1-(ε-oxoalkyl)pyridinium salts gives diastereomeric hydroxy compounds **86** and **87** in yields of 14–16% each (95AGE2007).

2.4.1.5 Ene reaction, Heck reaction, acyloin condensation (Scheme 23)

N-Alkenyl tetrahydroisoquinoline carbaldehydes cyclize in a *hetero-ene reaction* to afford azepino[1,2-*b*]isoquinolines **88a–c**, the stereoselectivity being highly dependent on the substitution pattern and the Lewis acid (04EJO3611): diastereomers **88a** and **b** form in the presence of boron trifluoride etherate in a ratio of 1:9, but under the action of chelating Lewis acids (SnCl$_4$, TiCl$_4$, ZnCl$_2$, EtAlCl$_2$) in the inverse ratio of about 9:1, together with minor amounts of other isomers. Analog **88c**, on the other hand, is exclusively formed, regardless of the type of the Lewis acid.
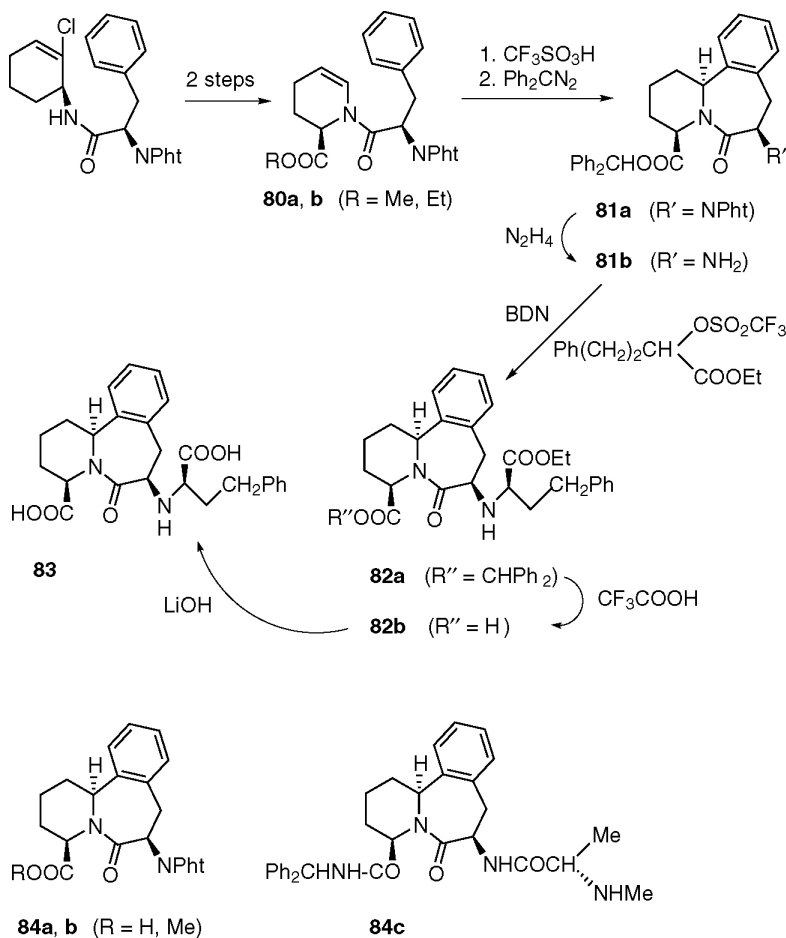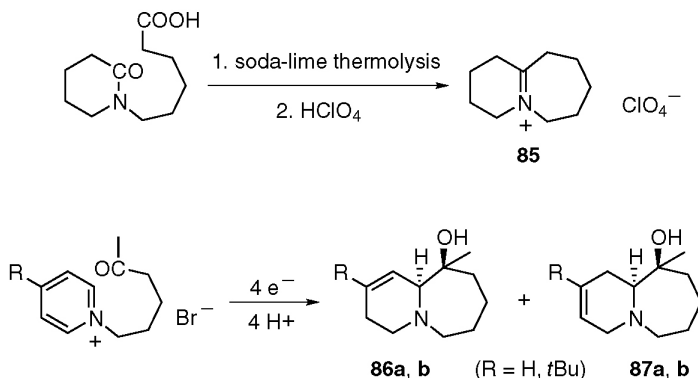
Scheme 21

The intramolecular Heck reaction of an iodobenzyl piperidone (*exo-trig* cyclization) affords a mixture of regioisomers **89a** and **b**, inseparable by flash chromatography (02S87). An analogous reaction gives lactam ester **89c** (96H(42)155).

Diester cyclization leads to acyloin **91** or the alternative tautomeric form (65T2961).

2.4.1.6 Ring-closing metathesis

The well-known method of olefin metathesis has since the 1990s found new applications, also in the presence of heteroatoms (00AGE3012, 09MI1). The precondition was the discovery of potent catalysts in
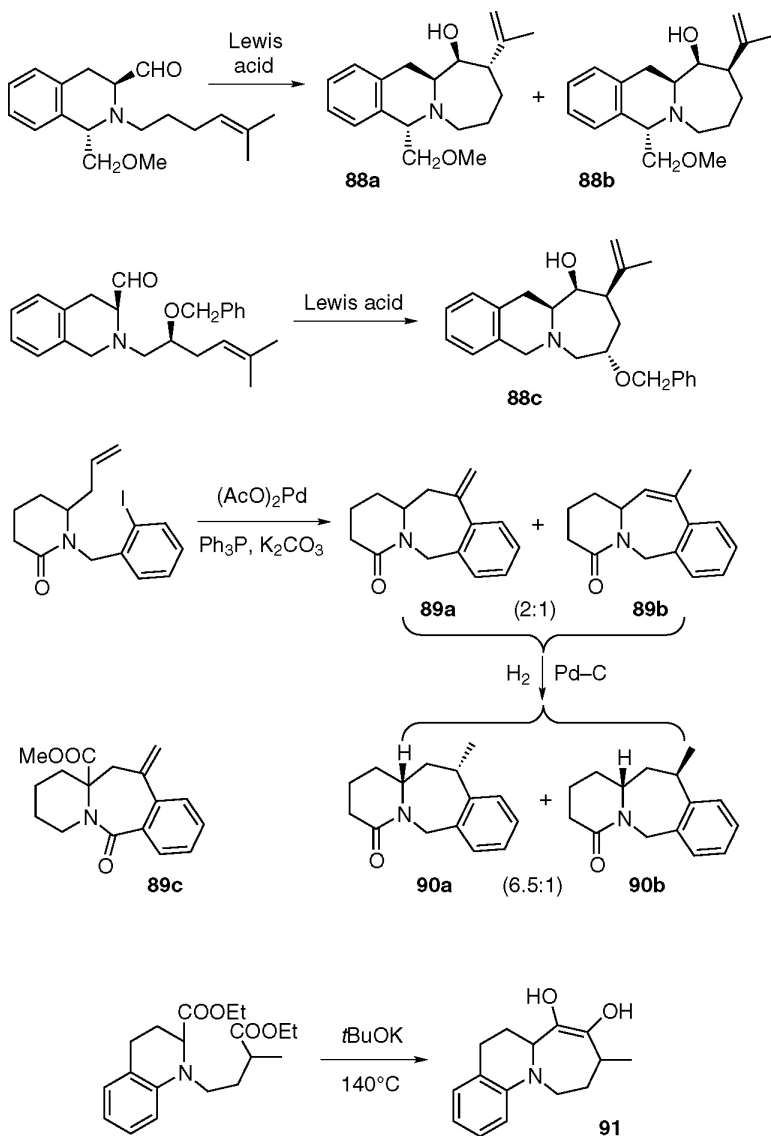
Scheme 22

the form of alkylidene complexes especially of molybdenum and ruthenium with bulky substituents by Schrock, Grubbs, and Hoveyda (catalysts **436–439**, see Scheme 96). The equilibrium, in the case of the ring-closing metathesis (RCM) of a diene, is shifted in the direction of the cyclization product because the released olefin (generally ethene) is volatile.

Relevant examples of RCM (Schemes 24 and 25) are based on the cyclization of nitrogen-linked α,ω-dienes (commonly lactams), the nitrogen atom being part of a piperidine ring. The yields are generally high. The cyclization of 1-pentenyl-2-vinylpiperidine derivatives affords lactams **92** (hence made from glutarimide in three steps) (96T7251) and **94** (01JOM9056) and even compounds **95a** (04JOC7114) and **95b** (10OBC2639). A 1-butenyl-2-allylpiperidine derivative gives lactam **93** (99J(P1)1695) while, in the case of the 1-pentenyl-2-styryl structure, the more reactive second-generation Grubbs catalyst (cat. Gr. II) was used to form lactam **96** (08PAC751). Finally, 1-allyl-2-butenylpiperidones are direct precursors of peptide-like lactams **97** (hence made from pyroglutamic ester in four steps) (04TL5987) and **98** (99SL1127).

2.4.2 By annulation onto the seven-membered ring

2.4.2.1 *N*-Alkylation and lactamization (Scheme 26)

Bicyclic ester **100** forms in analogy to isomeric ester **65** (Section 2.4.1.1) (07JOC5608). β-Phenylethylamine **101** undergoes palladium-catalyzed direct aromatic carbonylation, thus providing another synthesis of benzo-lactam **78b** (06JOC5951). A stereoselective nitro-Mannich/lactamization cascade of γ-nitro ester and cyclic imine affords polysubstituted lactam **102** (08OL4267).

Scheme 23

### 2.4.2.2 Enamine and iminium ion cyclization (Scheme 27)

The base-catalyzed [3+3] reaction of enamino ester with acrylic ester (**103b**) or more favorably acryloyl chloride (**103a**) by consecutive *N*-acylation and *C*-alkylation gives bicyclic lactam ester **104** (85S735). A
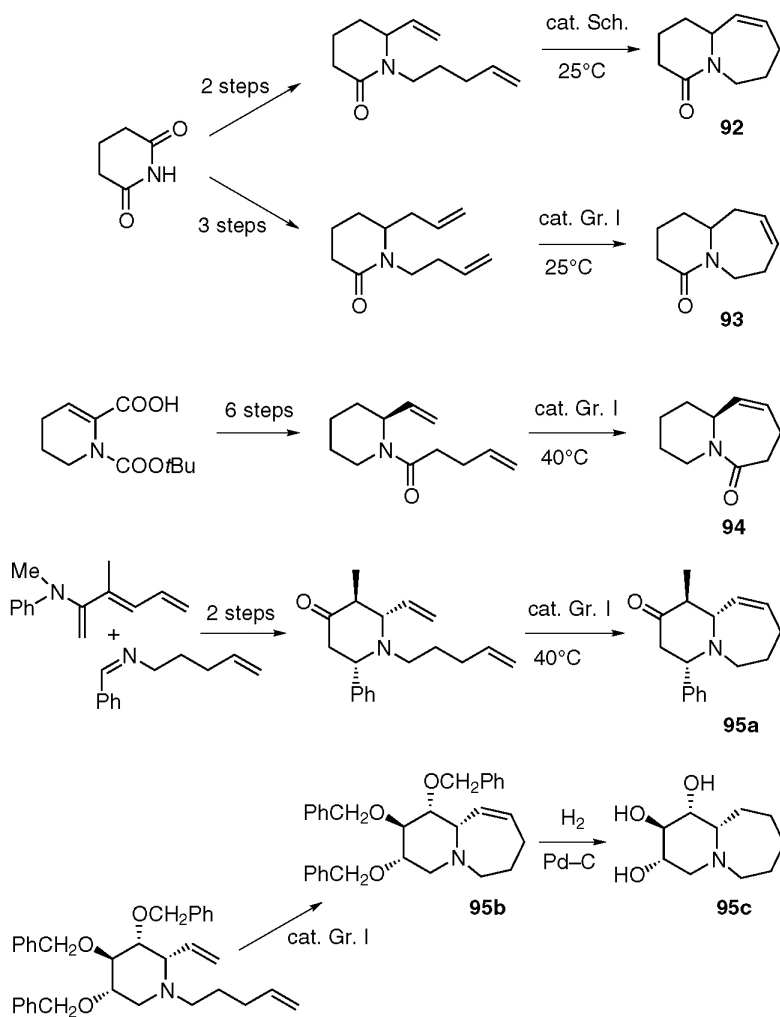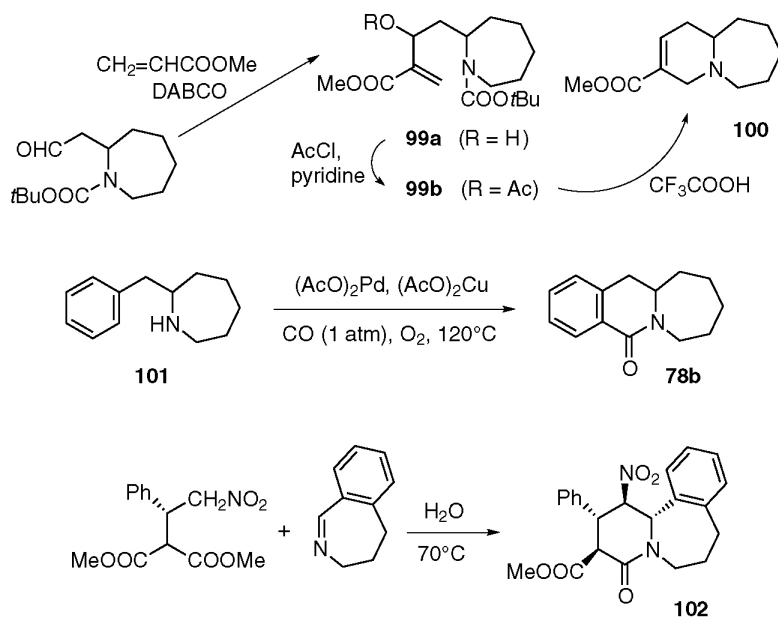
Scheme 24

similar reaction of *β*-nitroenamine without catalyst leads to regioisomers **105a** and **b** (08T5545).

Enamine **106** (derived from Meldrum's acid), in a process of mono-decarboxylating transesterification and subsequent intramolecular alkylation, is cyclized to form enamino ester **107** (90H(31)1251). The direct route by flash vacuum thermolysis does not work in the case of 6/7 bicyclic **107**. Methylene compound **109** originates (analogously to bicyclic **40b**) from
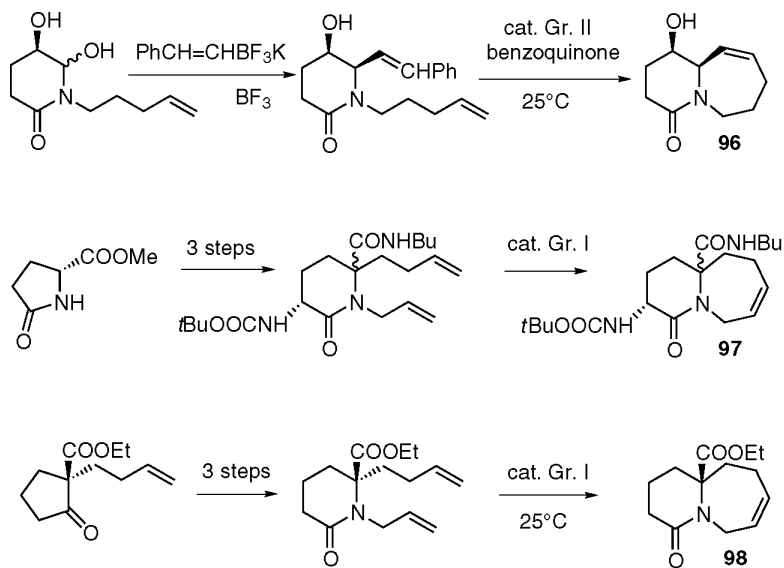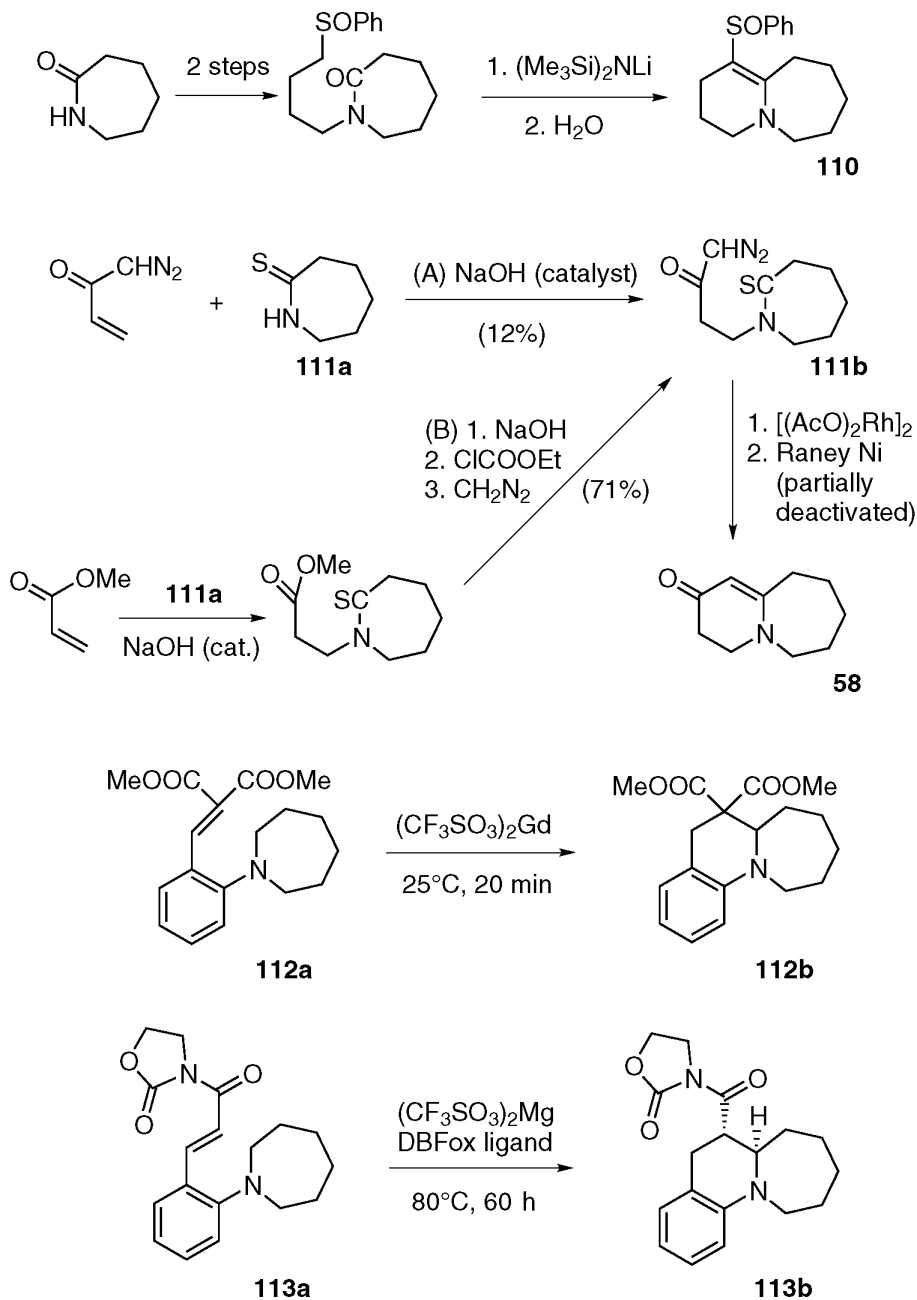
Scheme 25

Scheme 26
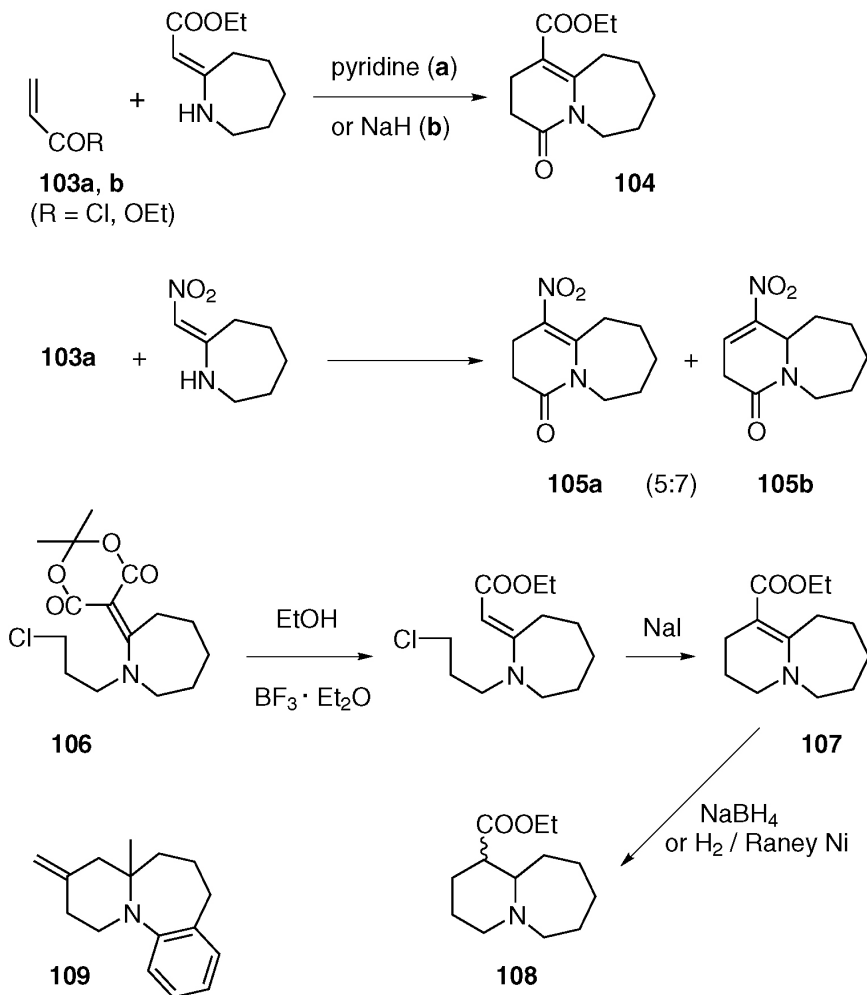
Scheme 27

α-tetralone oxime mesylate by an iminium ion Mannich-type cyclization (08BKC1669).

2.4.2.3 Carbon–carbon coupling reaction (Scheme 28)

Four-carbon annulation onto the caprolactam ring is accomplished by intramolecular nucleophilic addition of an α-sulfinyl carbanion to the carbonyl group in order to obtain sulfinoenamine **110** (03OBC3495). Moreover, thiocaprolactam (**111a**) and its Michael adduct **111b**, via

Scheme 28

diazo-thioamide coupling (*aza-Robinson annulation*), provide another route to ketoenamine **58** (89TL3625). Because of poor yield with direct procedure A, a second procedure B through Michael addition to methyl acrylate, hydrolysis, mixed anhydride formation, and conversion to diazoketone **111b** has been developed.

In an approach to functionalize relatively unreactive C–H bonds via catalytic intramolecular hydride shift/ring closure reaction cascade, using the *tert-amino effect*, alkylidene malonate **112a** was rearranged to isomeric tricyclic **112b** (09OL129). On the other hand, acyl oxazolidone **113a** enables an enantioselective sequence in order to yield derivative **113b** (09JA13226). In these two cases gadolinium triflate and a magnesium triflate/ligand combination, respectively, have proven to be superior to other Lewis acid catalysts.

2.4.2.4 Ring-closing metathesis (Scheme 29)

Six-membered ring-closing metathesis is based on azepine derivatives bearing terminal alkenyl groups at both N-1 and C-2 positions. Such reactions form (isomeric to **94** and **98**, respectively) lactams **114** (01JOM9056) and **115** (99SL1127).

2.4.3 By other approaches

Photolysis of an phthalimide leads, passing through imide-bond cleavage and cyclization, to ketolactams **116** and (after releasing butadiene) **117** (Scheme 30) (85J(P1)2025). Thermal rearrangement of α-(ε-azidopentyl) enones (e.g., **118**) produces enamides **119a** (in a mixture with **119b**) and **119c** (02TL5385).

Aminoester **121a** and isomeric indolizine **121b** (Scheme 31) are the products of the [1,2] and [2,3] rearrangement, respectively, of *ene–endo*-spirocyclic, didehydropiperidine-derived ammonium ylide **120** that was *in situ* prepared from the diazoester (05OL2075). Acyclic ω-iodo-
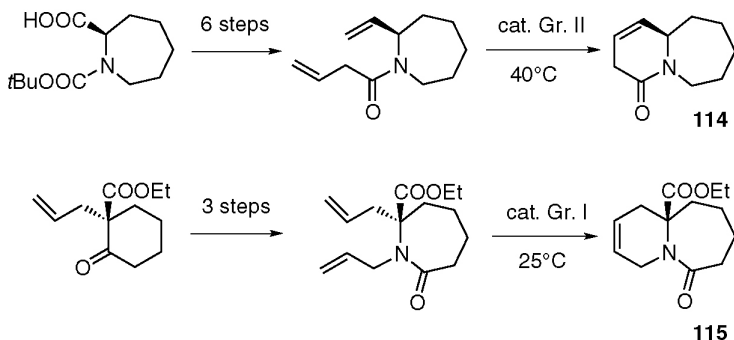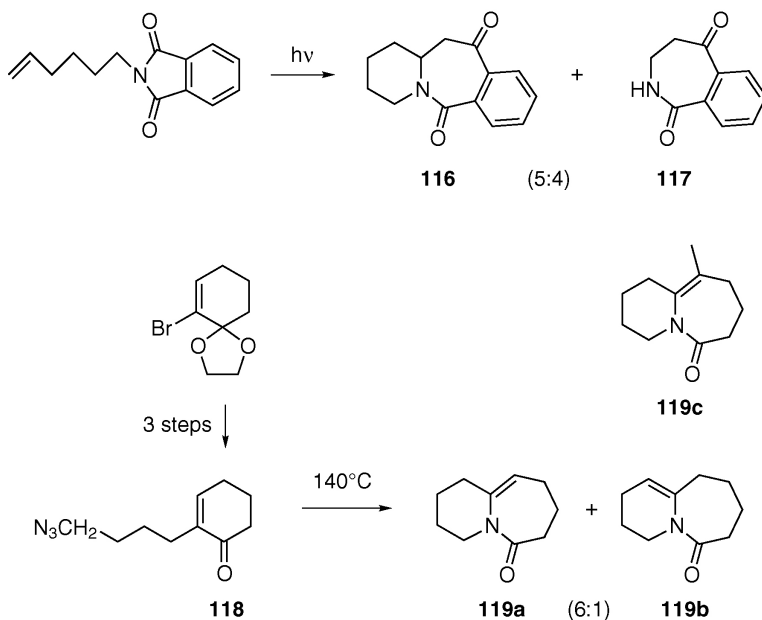
Scheme 29

Scheme 30

α,β-alkynoate **122** and 3-chloropropylamine undergo a process of sequential S_N2 reaction (of the amino group), Michael addition (to form the allenolate), S_N2 reaction (halogen-exchange), and S_N2 reaction (of the allenolate group) and give enaminoester **107** already mentioned (06T5697).

Moreover, octahydro compounds arise from the reduction (see Section 4.3) of higher unsaturated analogs, such as **8/9b/9d**, **124a** (see Scheme 32), **319a** (see Scheme 71) or **374a** and **b** (see Scheme 85), from the dehydration (see Section 4.4.3) of carbinol **24** or from the carbonylation (see Section 4.4.1) of enamine **133** (see Scheme 34).

2.5 Syntheses of hexahydropyrido[1,2-a]azepine derivatives

2.5.1 By annulation onto the six-membered ring

2.5.1.1 N-Alkylation and lactamization (Scheme 32)
Pyridone **123b** is obtained by cyclizing N-alkylation (86JOC2184). Two routes are available for the synthesis of dihydropyridine **124a** involving partial reduction of an electron-deficient pyridine: (A) stepwise Birch or sodium naphthalenide reduction, alkylation, and cyclization (01J(P1)1435) or (B) one-pot dearomatization/bisalkylation promoted by trialkylstannyl lithium via a *stanna-Brook rearrangement* (06OL951). Isomer **124b** forms analogously.
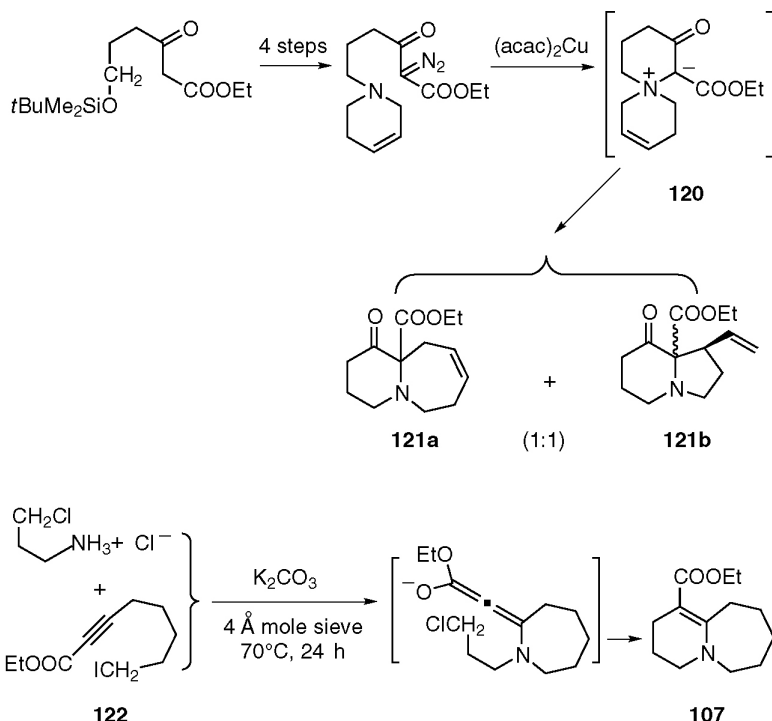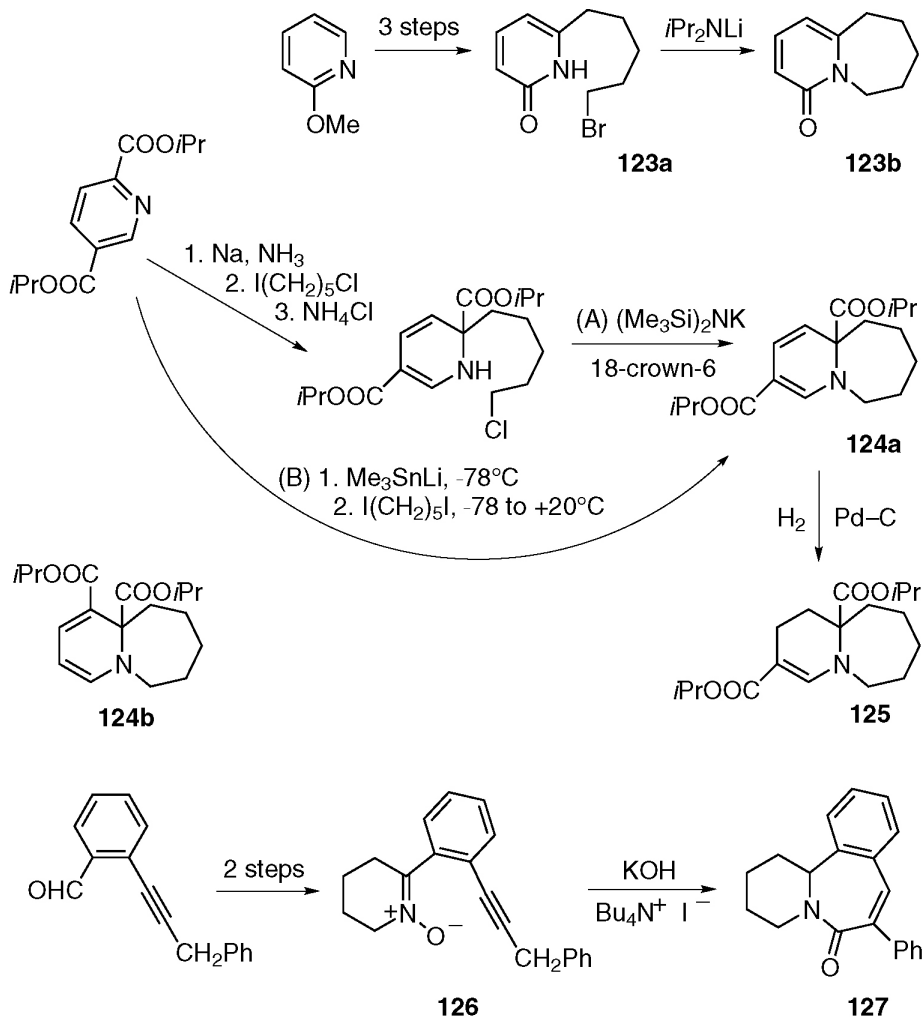
Scheme 31

A dipolar route of heterocyclization of a monocyclic enallenyl nitrone (from precursor **126** by base-catalyzed propargyl-allenyl isomerization) leads to lactam **127** (05EJO2715) that is an analog of astrocasine (**8**).

2.5.1.2 Azomethine ylide and iminium ion cyclization

Enaminone **128** (Scheme 33) is obtained, together with an isomeric indolizine derivative, by flash vacuum thermolysis of aminomethylene Meldrum's acid derivative through intermediate ketene and delocalized azomethine ylide (85TL833). The thermally induced cyclization of semicyclic dienamines to afford, for instance, tricyclic **129** is also believed to start with an azomethine ylide (97JOC7744); the *p*-chlorophenyl substituent is essential for the reaction. Unstabilized ylide **130**, on the other hand, is generated from pipecolinic acid and *β*-phenylcinnamaldehyde by the decarboxylation method; target base **131** is formed by 1,7-electrocyclization and [1,5]-hydrogen shift (99J(P1)2605).

In the series of ACE inhibitors (cf. Section 2.4.1.3) dihydropyridine **132** (Scheme 34) was cyclized to give pyridobenzazepine **133** (96WO19492).
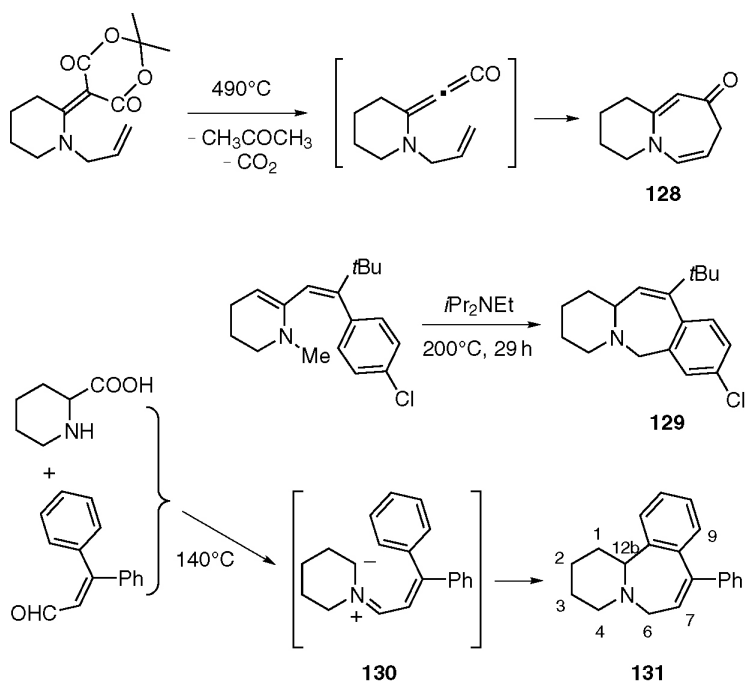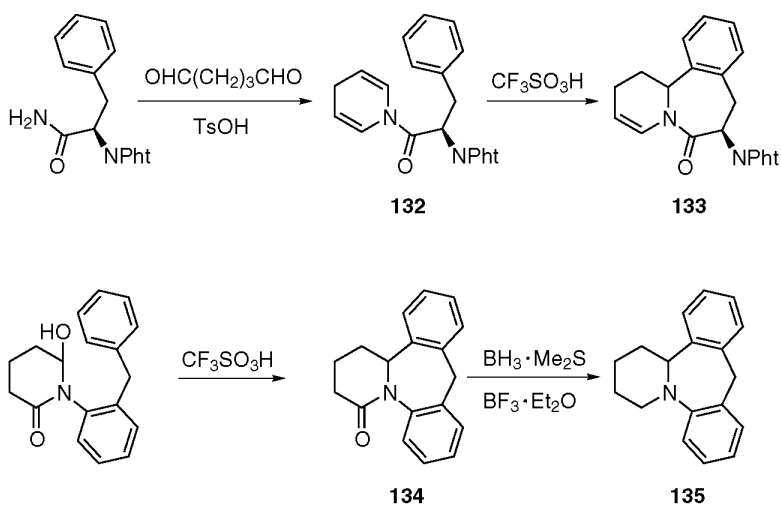
Scheme 32

Tetracyclic lactam **134** was similarly obtained from the hydroxylactam by *N*-acyliminium ion cyclization (01H(55)1519, 02BKC1623).

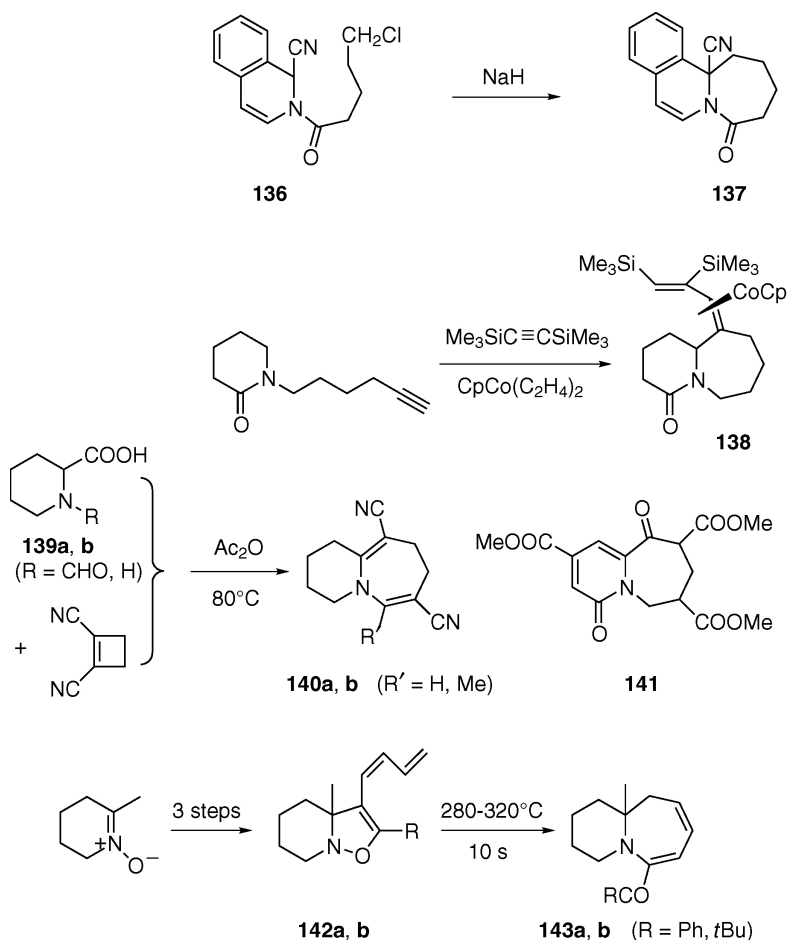### 2.5.1.3 Carbon–carbon coupling, cycloaddition, thermolysis (Scheme 35)

Cyclizing *ω*-chloro Reissert compound **136** gives rise to tricyclic lactam **137** (72JHC541). In a study of the cobalt-mediated reaction of pyridones with alkynes, in the case of the *N*-hexynyl compound, C–H activation with
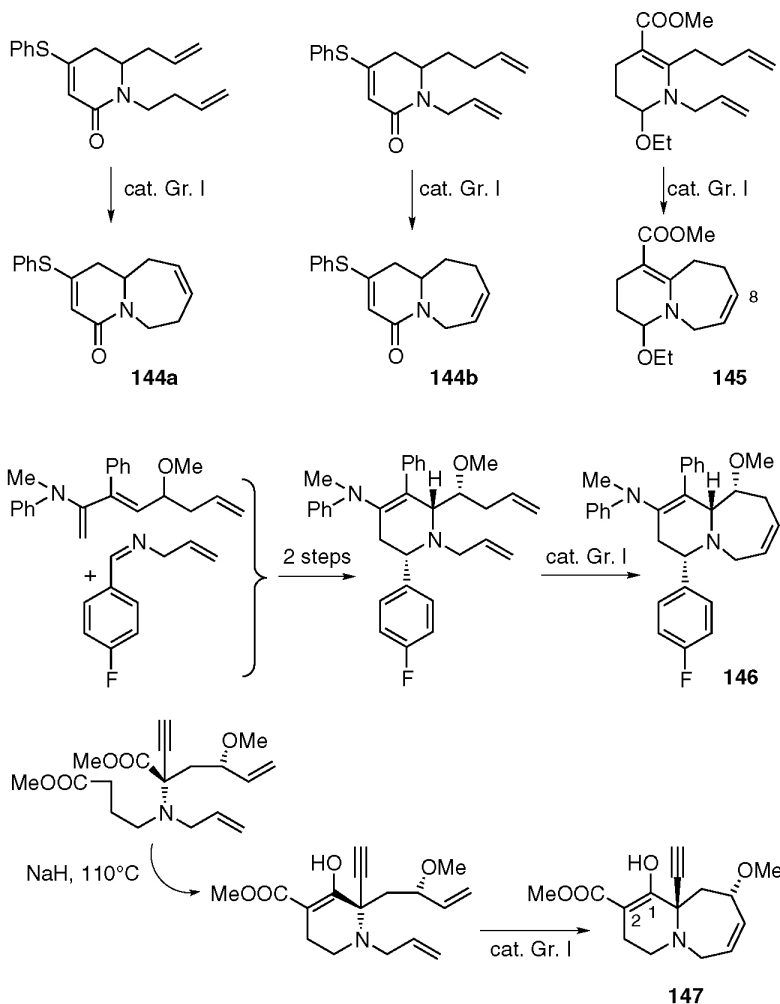
Scheme 33

Scheme 34

Scheme 35

simultaneous double alkyne stitching predominates to give diene complex **138** in addition to a cyclobutadiene complex (07CEJ7443).

Cyclic amino acids **139**, when heated in acetic anhydride, probably form initially mesoionic oxazolium 5-oxides (munchnones); subsequent 1,3-dipolar cycloaddition of 1,2-dicyanocyclobutene, loss of carbon dioxide, and opening of the cyclobutane ring lead to dinitriles **140** (80JHC1593). Pyridone **141** is the by-product (together with an indolizine) of the mono-cyclic pyridone dicarboxylate and acrylic ester (73JHC77).

The thermal transformation of 2,3-dihydroisoxazoles **142** leads to α-acylenamines **143**; the proposed mechanism again involves azomethine ylides (01T4349).

Scheme 36

2.5.1.4 Ring-closing metathesis

Bicyclic dienic products recently synthesized by this method (Scheme 36) are lactams **144a** and **b** (07T8267) and enamine ester **145** (09CEJ4565). The precursor of the latter substance originates from a four-component synthesis followed by γ-allylation. The alternative γ-propargylation and subsequent *ring-closing enyne metathesis* performed under an ethene atmosphere lead to the 8-vinyl derivative of product **145**.

Other examples are those of polysubstituted chiral compounds **146** (formed together with a minor diastereomer) (04JOC7114) and **147**

(06AGE2731). (Product **146** during its synthesis, unlike analog **95a**, does not suffer acid hydrolysis of the *N*-methylanilino group after the aza-Diels–Alder reaction.) Ethynyl enol **147** is isolated in a very small yield; the corresponding (2*S*)-*tert*-butyldimethylsilyloxymethyl compound exists in its tautomeric 1-keto form.

The use of the second-generation Grubbs catalyst or the Grubbs–Hoveyda catalyst (cat. Gr. H.) (Scheme 37) enables the synthesis of benzo-fused lactams **148** (09TA1154), **149** (05JOC5519), and α-amino-α,β-unsaturated lactam **150a** (08TL5141).

2.5.1.5 Pathways to homoberbines

Several kinds of dibenzo-fused pyrido[1,2-*a*]azepines (isoquinobenzazepines) have been the subjects of intensive synthetic and pharmacological studies, partly as a consequence of their structural similarity to ring-homologous berbine alkaloids and papaverine. The parent structures of these homoberbines (69HCA1228) are as follows (Formulas **151**, Scheme 38), in a classification given by Meise et al. (99PHA658):

- (**151K**) K-type, B-homoberbine, isoquino[3,2-*a*][2]benzazepine
- (**151L**) L-type, *iso*-B-homoberbine, isoquino[3,2-*b*][3]benzazepine
- (**151M**) M-type, C-homoberbine, homoprotoberbine, isoquino[2,1-*b*][2] benzazepine (cf. **6**)

Scheme 37

151K   **151L**

151M   **151N**   **151P**
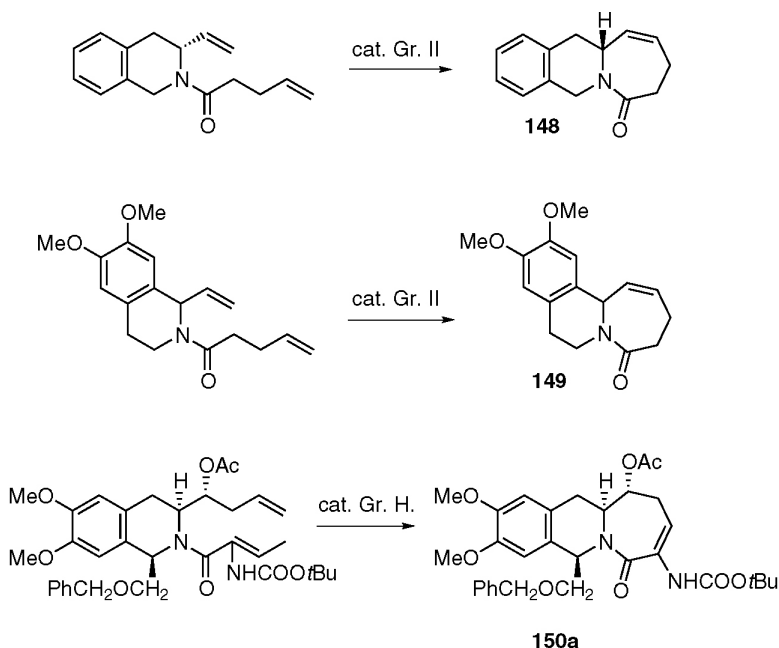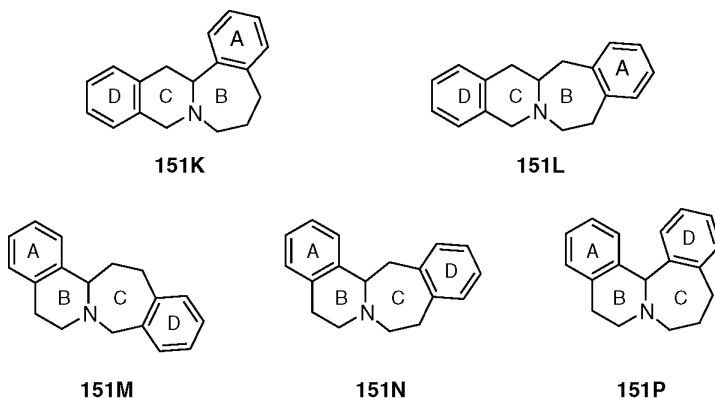
Scheme 38

- (**151N**) N-type *iso*-C-homoberbine, isoquino[1,2-*b*][3]benzazepine
- (**151P**) P-type, homo-isoberbine, isoquino[1,2-*a*][2]benzazepine (also O-type)

Relevant synthetic methods for the annulation of a benzo-fused seven-membered ring onto an existing benzo-fused six-membered ring are available with M-, N-, and P-types.

(a) *M-Type* (**151M**). A first method is the *Pictet–Spengler reaction* (Scheme 39), an application of the Mannich reaction to β-phenylethyl-amines or, in this special case, to 1-phenylethyl tetrahydroisoquino-lines. Typical syntheses are those of homoberbines **155** (71T1363) and **157a** and **b** (69HCA1228). (Thin-layer chromatographic R_F values were tabulated.) N-Acyl-β-phenylethylamines (such as **152**) undergo the *Bischler–Napieralski cyclization* followed by reduction of the imi-nium salt (e.g., **153**) and Pictet–Spengler reaction of hydrohalides **154** or **156a/b**, respectively. The application of this latter cyclization to chiral precursor (1*S*)-**156a** gives pentamethoxy homoberbine (14a*S*)-**157a** (87CJC2356, 03CPB951, 05M1619).

In a second route *phenolic cyclization* (in the absence of acid) takes place at the *o*-position to the hydroxyl of precursor **159** to afford homoberbine **160** (Scheme 40) while the Pictet–Spengler reaction mentioned before yields isomer **161** (69JC874).

A third method is exemplified by the cyclization of N-oxide interme-diate **162** to give isomers **163** and **164**; they are analogs of couple **160/161** and can just like these be independently obtained from a 1-phe-nylethyl tetrahydroisoquinoline (80H(14)817).

A fourth approach is based on homophthalide isoquinolines, such as imine **165** (Scheme 41, upper part), and leads to the functionalization at the
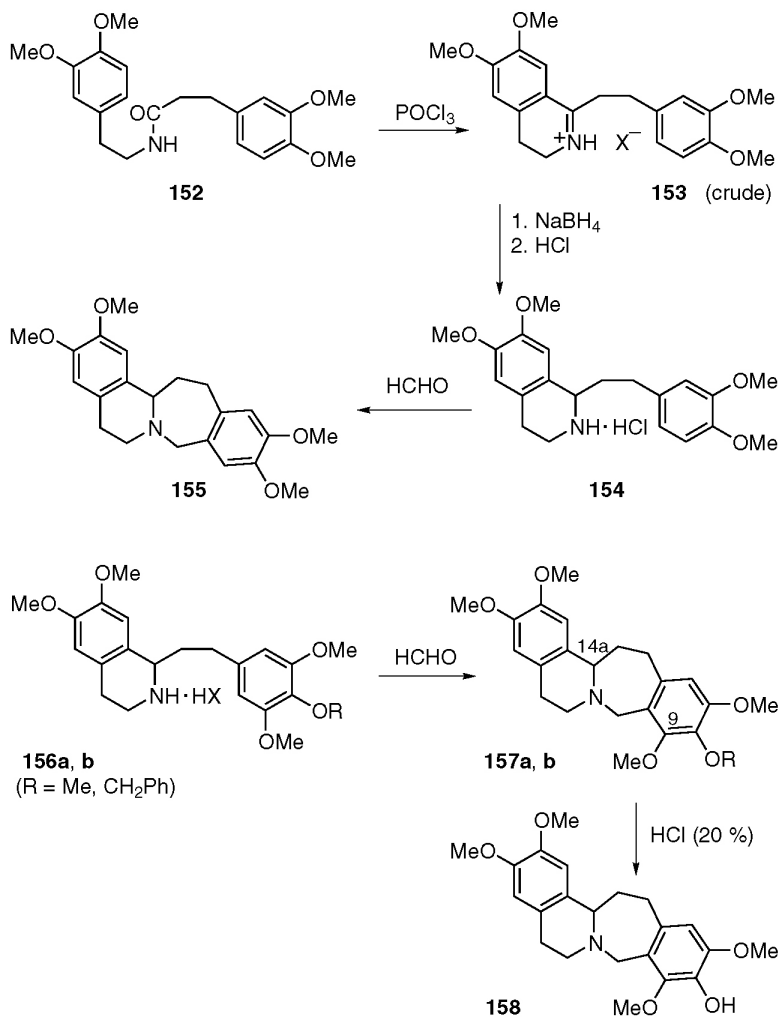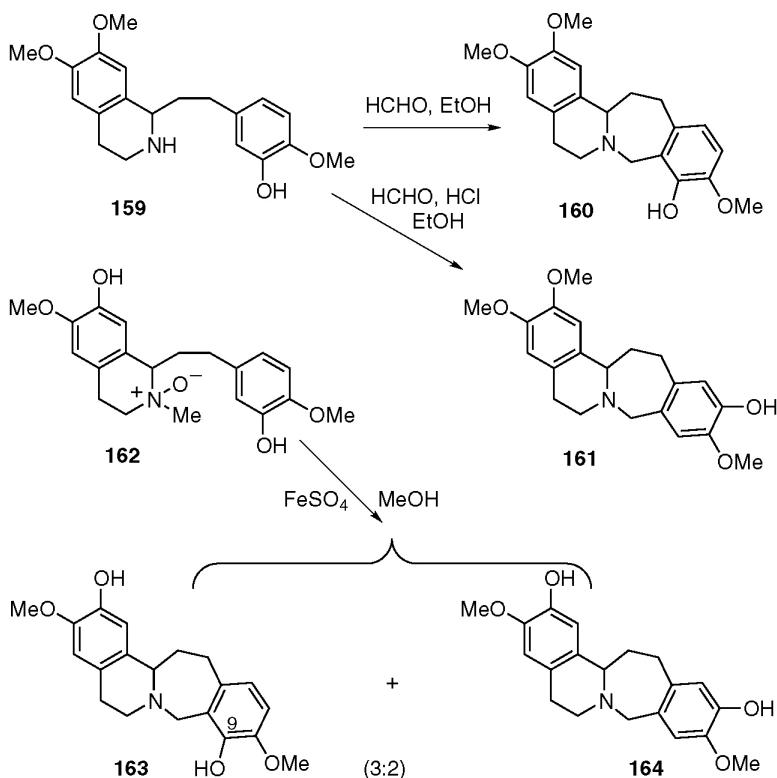
Scheme 39

13-position (71T1363). Hydrogenation provides a mixture (1:1) of diaster-
eomers **166**, further alkaline lactone ring cleavage with the mixture fur-
nishes a mixture (7:1) of lactams **167**; these are directly obtained (in a ratio
of 10:1) by the reduction of imine **165**.

A fifth route (Scheme 42) proceeds from amide **172** (comparable to **152**)
by intramolecular alkylation of the iminium salt to homoberbine **173**
(94LA1135).

Finally, the sixth approach by Dieckmann condensation leads to keto
derivative **174**, thus providing functionalization at C-14 (71T1363).

Scheme 40

(b) *N-Type* (**151N**). Homoberbine **177b** (Scheme 43) is isomeric to M-type derivative **173** and available by an analogous two-step synthesis from amide **176b** (97LA447). Unactivated precursor **176a** requires harsher conditions or temporary hydroxyl protection (mixed carbonate). The seven-membered rings of lactams **178b** and **c** are built by intramolecular lactamization (92JHC11).

(c) *P-type* (**151P**). Derivatives **179** and **181** (Scheme 44) can be constructed using both the routes known from N-type analogs **177b** and **177a**, respectively: the two-step synthesis leads to parent substance **179** (99PHA658) while mixed ester **180b** in a one-pot reaction sequence gives **181** (07JME4528). Ketone **182** is obtained by the Friedel–Crafts reaction (73USP3780043).

2.5.2 By annulation onto the seven-membered ring

2.5.2.1 Enamine cyclization (Scheme 45)

Heterocyclic secondary **183**-type enamines (exocyclic vinylogous urethanes) show ambident bisnucleophilicity; their nucleophilic reaction
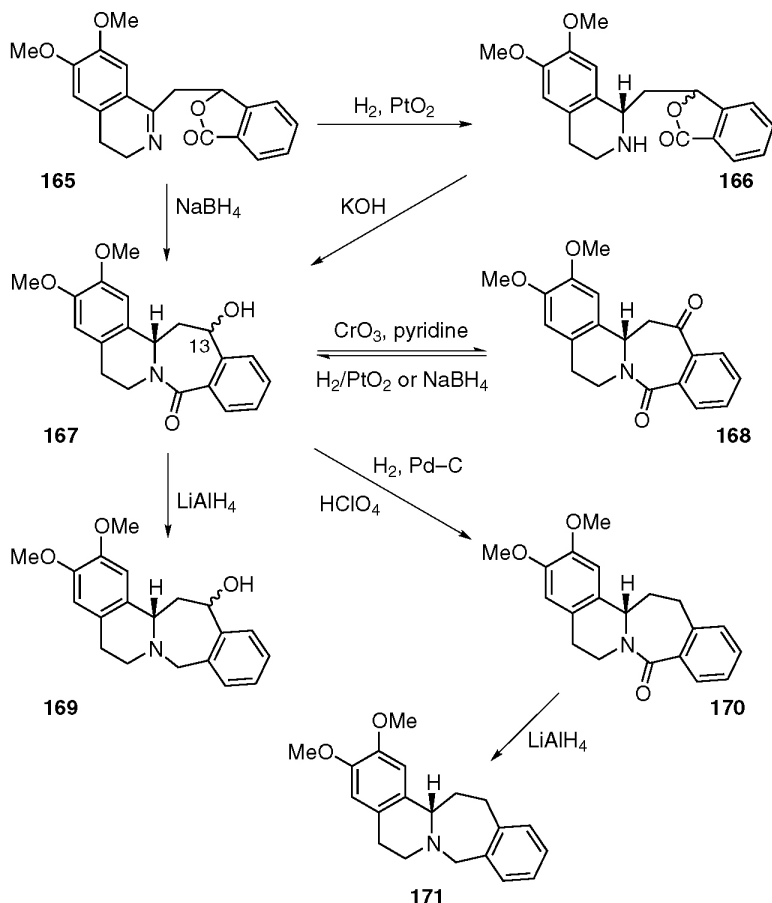
Scheme 41

can take place at the site of enamine carbon and/or amine nitrogen (02T2821). This situation will be exemplified by the annulation onto α,β-unsaturated carbonyl compounds, dicarboxylic acid chlorides, and other substances.

In this way, the Michael addition of enamines **183** onto aralkylidene acetoacetic ester or the three-component condensation of aldehydes, β-diketone, and enamine leads, by a modified Hantzsch pyridine synthesis, for example, to esters **184** and **185**, respectively (73DEP2210633, 77LA1888). The same enamines combine with masked acetoacetic ester **186** to give bis-enaminone **187** (91MI1, 92MI1); their reaction with cinnamaldehyde was described in terms of an aza-[3+3] annulation yielding dihydropyridine **188c** (08T883).
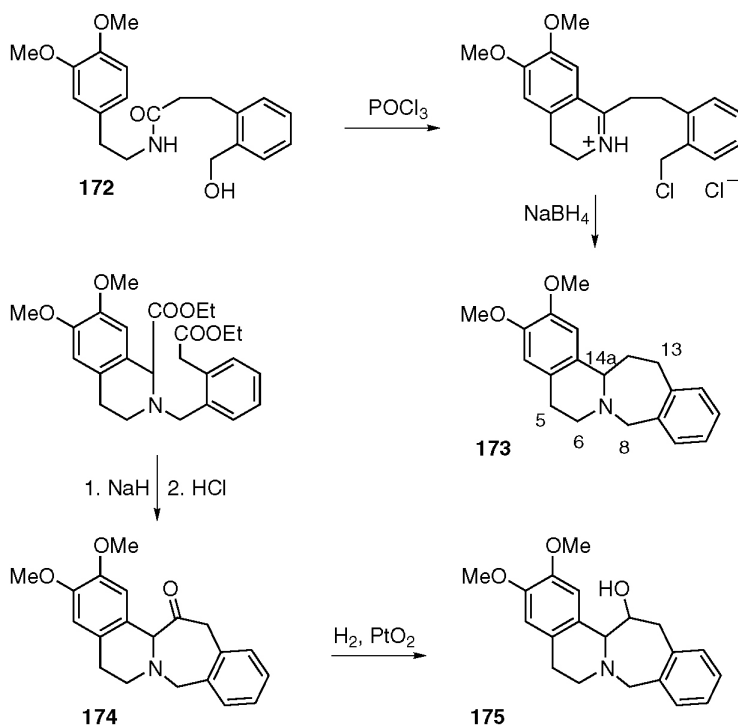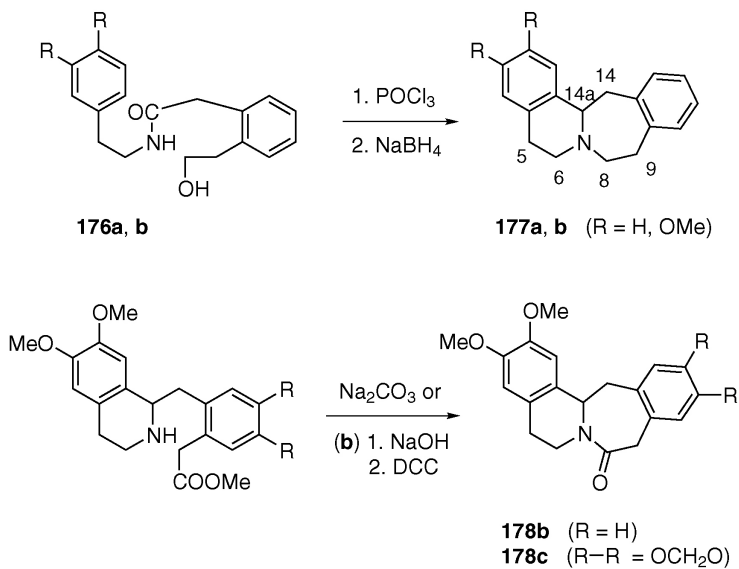
Scheme 42

Among dichloro bis-electrophiles, malonyl chloride with enamine **183b** affords pyridone **189**, probably resulting from *C*-alkylation and cyclocondensation followed by aromatization (02T2821). Finally, *o*-chloro-benzoylchloride leads to *C*-benzoylation and subsequent intramolecular substitution of the isolable intermediate to yield quinoline **190** (03ARK (is.2)146).

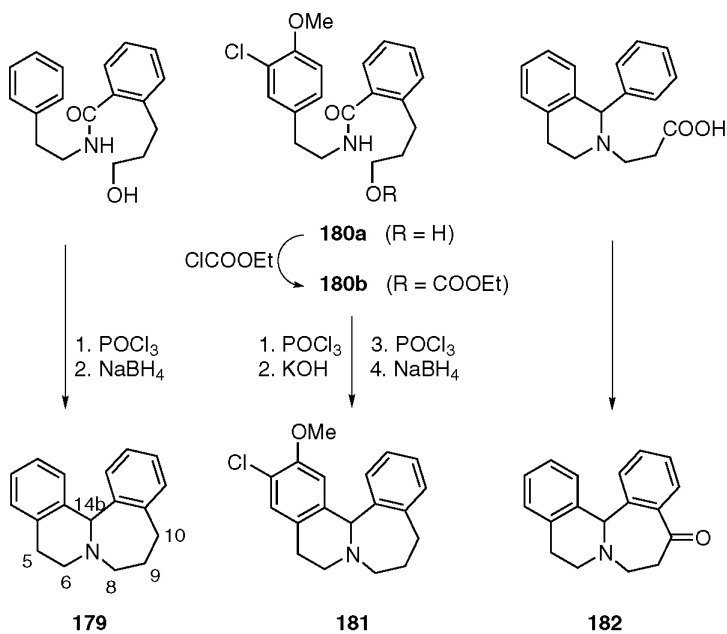### 2.5.2.2 Reactions of caprolactim ethers (Scheme 46)

Dimethyl acetonedicarboxylate (72IJC323) or cyanoacetone dianion derived from 5-methylisoxazole (85TL259) condense with caprolactim ether **191a** to afford pyridones **192a** (cf. **189**) and **194**, respectively. The condensation of *o*-halobenzoylacetic esters and caprolactim ethers **191a** or **b** leads similarly to quinolones, for instance, on an alternative route to aforementioned ester **190** (80JHC1729, 90KFZ(is.7)24).

2.5.2.3 Cycloaddition and cyclocondensation (Scheme 47)

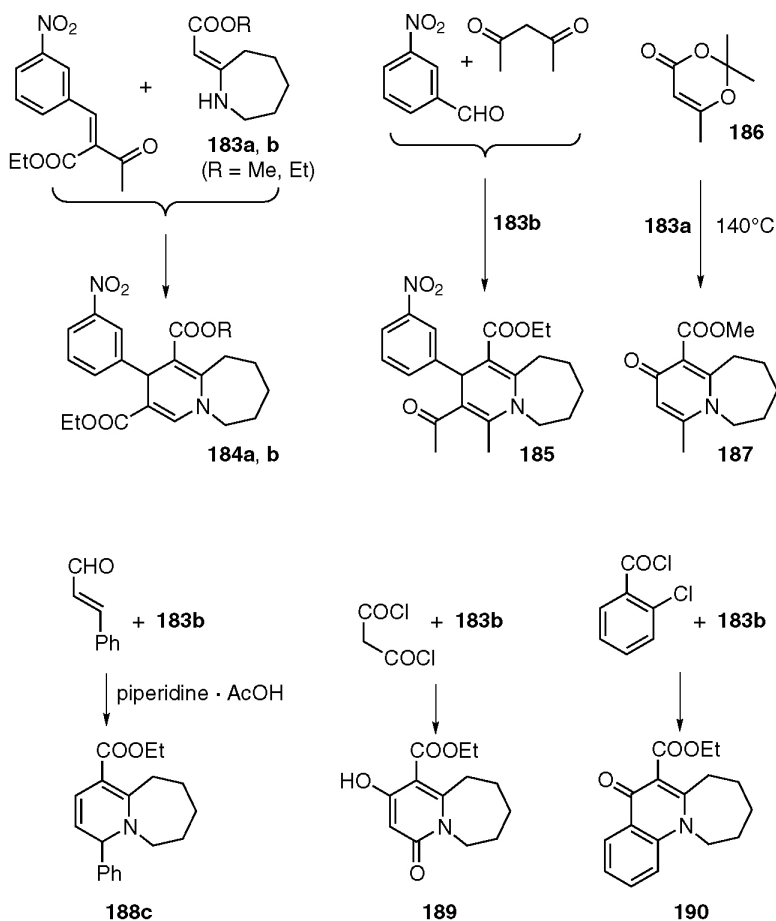*exo*-Cyclic secondary enamines **195** react with electron-deficient acetylenic esters via the Michael addition pathway followed by base-catalyzed

176a, b → **177a, b**   (R = H, OMe)

1. POCl₃
2. NaBH₄

178b   (R = H)
178c   (R—R = OCH₂O)

Na₂CO₃ or
(**b**) 1. NaOH
2. DCC

Scheme 43

180a   (R = H)
180b   (R = COOEt)

ClCOOEt

1. POCl₃
2. NaBH₄

1. POCl₃
2. KOH

3. POCl₃
4. NaBH₄

179   **181**   **182**
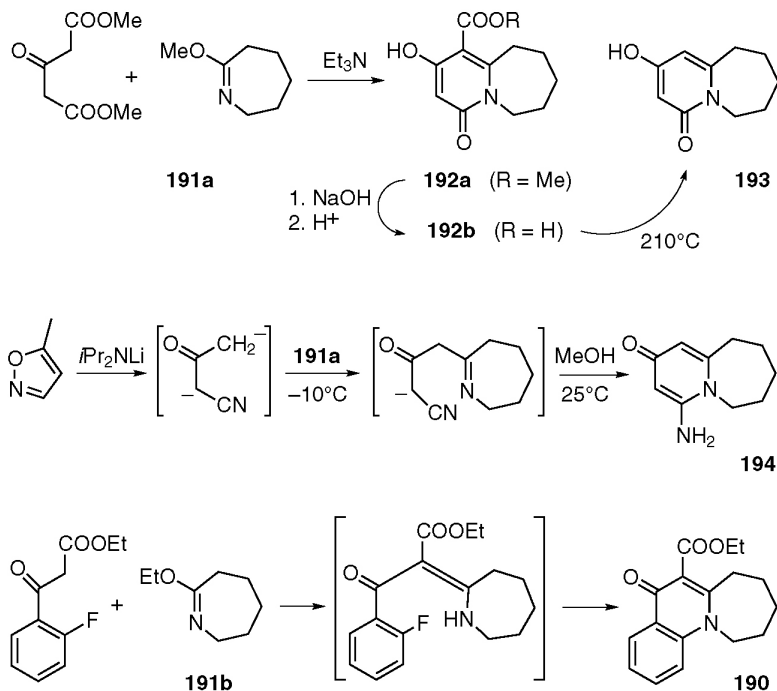
Scheme 44

Scheme 45

cyclocondensation to produce pyridones **196a–c**, the synthesis, in the case of ester **196a**, also succeeding in a one-pot operation (99T14611). Caprolactam **197** is believed to change into mesoionic intermediate **198** (*isomunchnone*) that is trapped by dimethyl acetylenedicarboxylate to give, after rearrangement, diester **199** (85JA5817).

Isoquinolone **200** is the result of a palladium-catalyzed carboxamidation/aldol condensation cascade of *o*-iodophenylacetic ester, caprolactam, and carbon monoxide (08OL4987).

2.5.2.4 Pathways to homoberbines

Syntheses based on an existing benzazepine framework are known in the series of K-, L-, N-, and P-types.

Scheme 46

(a) *K-Type* (**151K**). β-Phenylethylamines **201** (Scheme 48) can be cyclized either directly by the Pictet–Spengler reaction (76HCA623, 76HCA2059) or in two steps by formylation and subsequent Bischler–Napieralski reaction (77CPB2510) to yield homoberbines **202**. Such compounds can also be obtained by the Bischler–Napieralski reaction of amides **203** through iminium salts **204** unless these amides lack activating substituents in the future A rings (95LA567).

(b) *L-Type* (**151L**). Another Pictet–Spengler reaction (Scheme 49) gives homoberbines **205** (97H(45)2137). Increasing the paraformaldehyde excess up to 10 equivalents results in the formation of a mixture of the 1- and 3-hydroxymethyl derivatives of product **205a**.

(c) *N-Type* (**151N**). Homoberbine **206** was recently synthesized under acid-mediated conditions via intermediacy of an iminium ion undergoing the favored 6-*endo-trig* cyclization (09T351).

(d) *P-Type* (**151P**). Homoberbines, such as **209** (Scheme 50), are obtained, analogously to derivative **181**, in a four-step one-pot synthesis from protected amides **207** (87LA639, 03H(60)887). All three intermediates of derivative **209b** including iminium salt **208b** could be isolated and characterized (88LA1099).
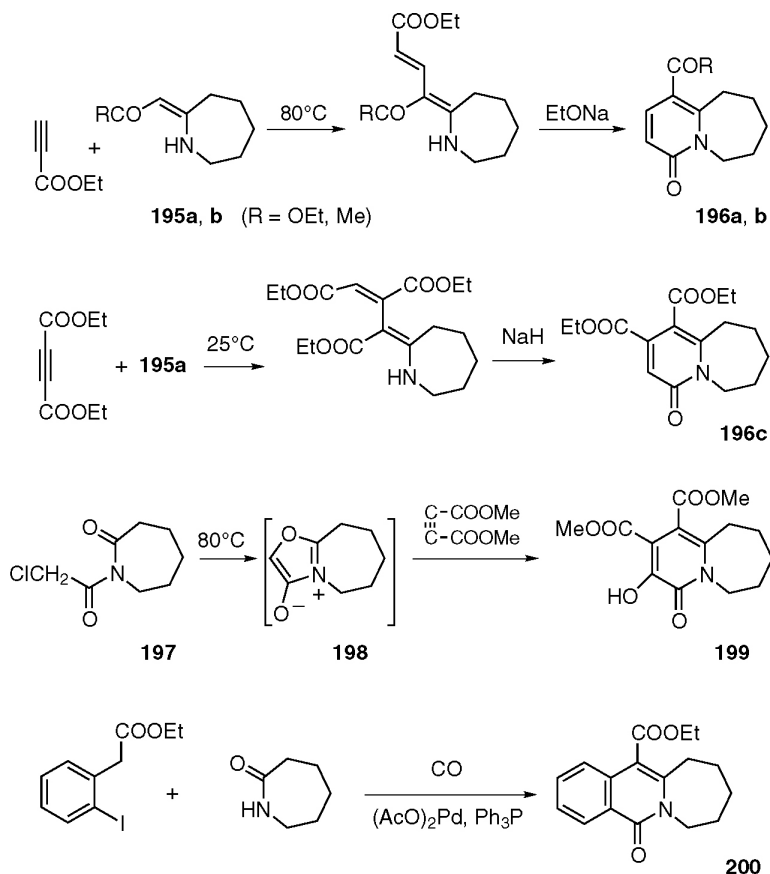
Scheme 47

### 2.5.2.5 Isoquino[2,3-b][2]benzazepines
The tetracyclic framework of homoberbine-like compound **210** was constructed by Beckmann rearrangement, reduction, and Pictet–Spengler cyclization (86JHC975).

2.5.3 By other approaches

2.5.3.1 Ring expansion and allene cyclization (Scheme 51)
The thermal rearrangement of azidobutylbenzoquinone **211** gives a small yield of enamide **212** (87TL4929). The formation of lactam **213** is an example of a palladium-catalyzed heteroannulation cascade involving the generation of a (π-allyl)palladium intermediate followed by regioselective intramolecular nucleophilic addition of malonate (01CC964).
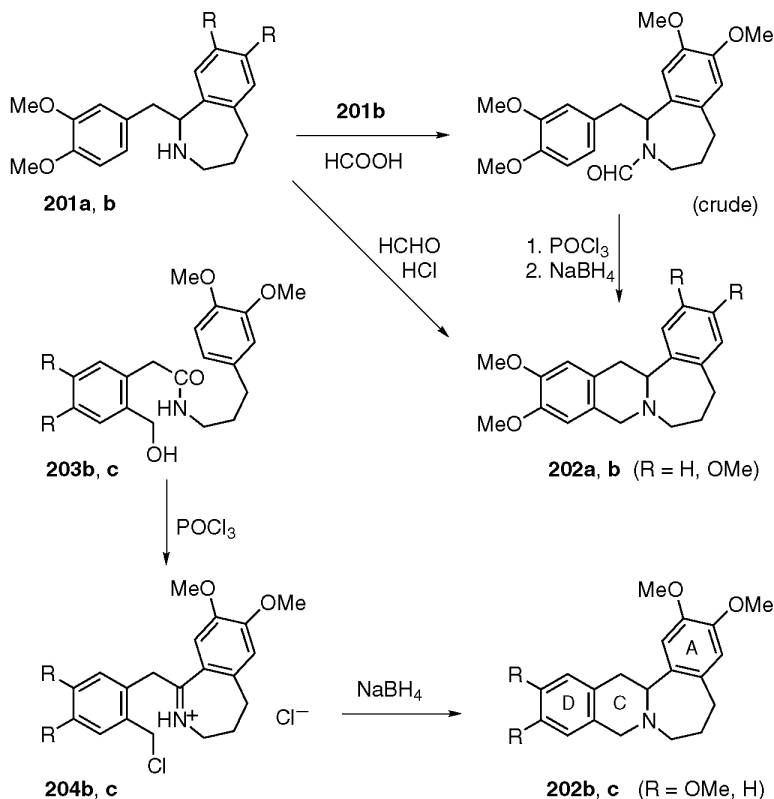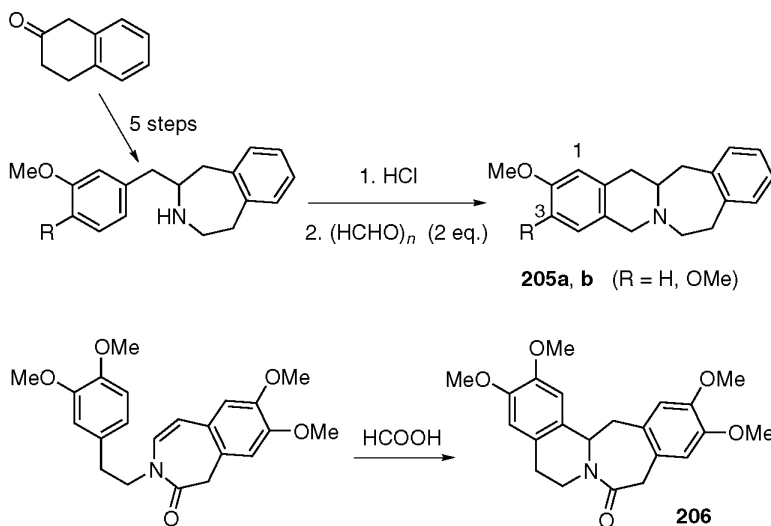
Scheme 48

2.5.3.2 Ring-closing metathesis

The double ring-closing metathesis of tetraenes (Scheme 52) is exemplified by the reaction of amide **214** that leads either to an inseparable mixture of lactams **216a** and **b** together with monocyclic amide **215** and another product or exclusively to the lactams, depending on the catalyst used (04CEJ3286). Trienyne **217** gives in a similar manner 1,3-dienic lactam **218** (04JOC6305).

Both dienic enamide **220a** and its homolog **220b** (obtained by base-promoted isomerization of the respective propargylamides **219a** and **b**) afford in a tandem RCM mixtures of 1,3-dienic lactams **221** and **222**, though in different proportions (02OL2417).

A method of *diversity-oriented synthesis* consists in sequencing *multicomponent reactions* with subsequent transformations that further increase molecular complexity. Thus, amides **223a** and **b** (Scheme 53, both obtained
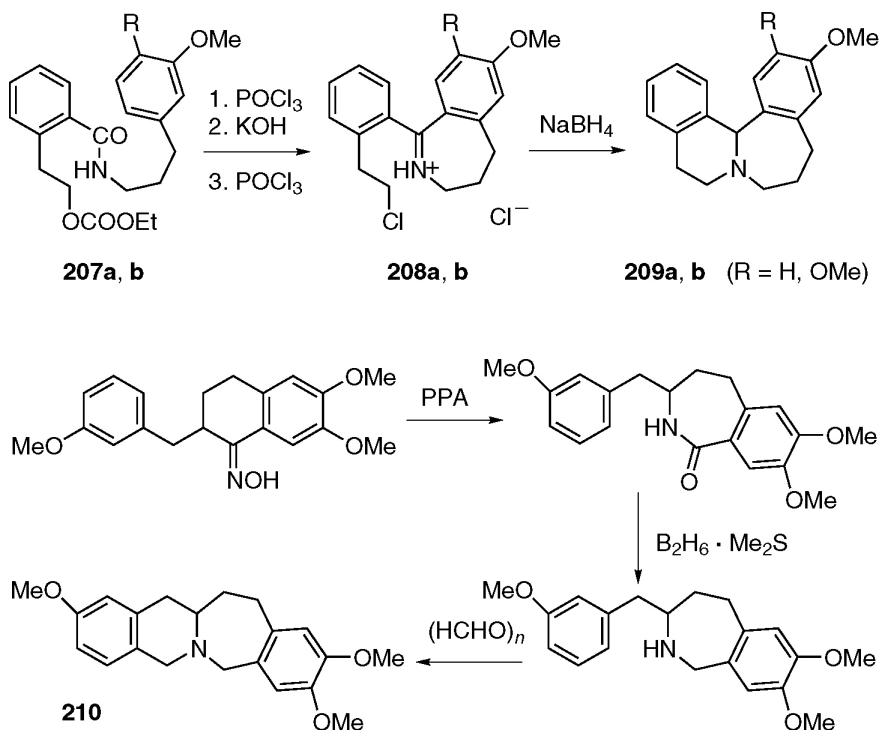
Scheme 49

by four-component reactions) furnish, by RCM/Dieckmann cyclization or by an enyne RCM/cross metathesis cascade (with styrene as a fifth component) and Dieckmann cyclization, respectively, lactams **224a** and **b** (09T6454). Cyclization, in the case of analog **223c**, in a reversed order (i.e., via Dieckmann reaction followed by RCM) provides lactam **224c** in an optimum yield.

2.5.3.3 Pathways to N-type homoberbines

The pathways (Scheme 54) start from macrocyclic or pyrroloazepine precursors: with *cis–trans* isomeric silylated stilbene lactams **225a** and **b**, intermediary reduction of the amide to an amine functionality triggers a regioselective [7,6] transannular cyclization to position isomers **177b** and (through **226a**) **226b**, respectively (99JOC4830). The ring expansion of isoindolobenzazepine **227**, on the other hand, proceeds by quaternization and Stevens rearrangement to give nitrile **228a** together with some dehydrogenation product **228b** (01CCL7).

2.5.3.4 Reduction

Hexahydro compounds are obtained by the reduction (see Section 4.3) of higher unsaturated analogs, such as **228b**, **246/248** (see Scheme 58), **256** (see Scheme 59), **269a/b** and **270b** (see Scheme 61), and **342** (see Scheme 78).
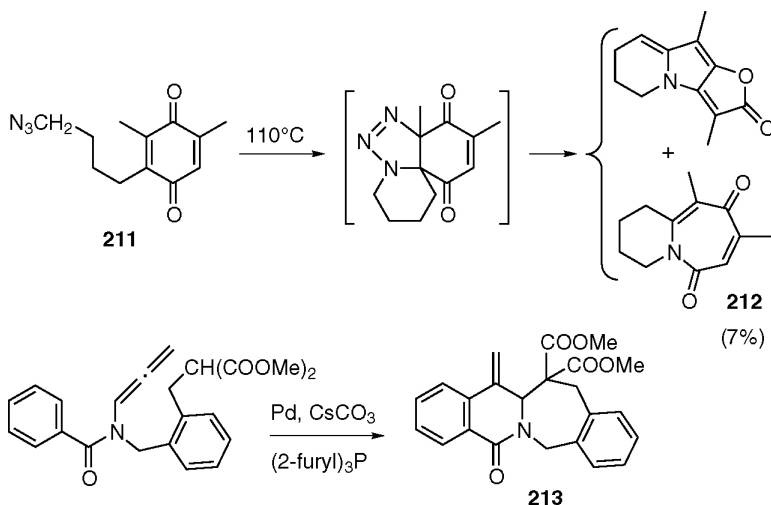
Scheme 50

2.6 Syntheses of tetrahydropyrido[1,2-a]azepine derivatives

2.6.1 By annulation onto the six-membered ring

2.6.1.1 Alkylation and amidation

Tetrahydroazepine-fused pyridinium salts **229a** (61TH1) and **230a** (99M783) form by intramolecular S_N reactions of 2-(ω-halopentyl)pyridines (Scheme 55). Another example may be found below (**303** from **302**, Scheme 69). Attempted dehydration of alcohol **229a** as known with the quinolizinium series (59JCS1686) failed and lead instead to acetate **229b**. Pyridoazepinium salts **230** (e.g., **230b**) also form on an inverse route involving the intramolecular free-radical substitution of the pyridinium ring (91T4077).

(ω-Chlorobutyryl)acetonitriles, such as **231a** (Scheme 56), are not intramolecularly cyclized unless in the presence of diazomethane (via enol

Scheme 51

ether **231b**) (81MI1) or better of base (83SUP1027166) in order to yield polycyclic enaminones **232** and **233**.

Mild thermolysis of azidoquinone **234** gives ring-contracted cyclopentenedione **235** (87TL4929) that under harsher conditions undergoes further rearrangement to ring-expanded isomer **236a** and the corresponding dehydrogenation product **236b**. In the presence of acid isomeric styryl structure **236c** is favored.

2.6.1.2 Ring-closing metathesis

In the field of dihydropyridines, chiral difluoro ester **237a** was obtained by RCM (10OL3484) whereas simpler **237b**-type esters could even be composed from acyclic starting materials in an efficient one-pot protocol (four-component-reaction/γ-alkylation/RCM/elimination sequence) (10JCO713).

2.6.1.3 Enamine and iminium ion cyclization

Heterocyclic secondary enamines and dicarboxylic acid dichlorides undergo complex, ring-size-dependent annulation reactions that, in the case of ester **238** and phthaloyl chloride (Scheme 57), lead to lactone-containing derivative **239** (02T2821).

Quaternary salts (e.g., **241a–c**) of diphenylvinyl dihydroisoquinoline **240** when deprotonated generate stabilized $\alpha,\beta;\gamma,\delta$-unsaturated azomethine ylides; 1,7-electrocyclization and subsequent 1,5-hydrogen shift give tetracyclic compounds **242a–c** (03TL793, 05S2039, 06T5725). Starting
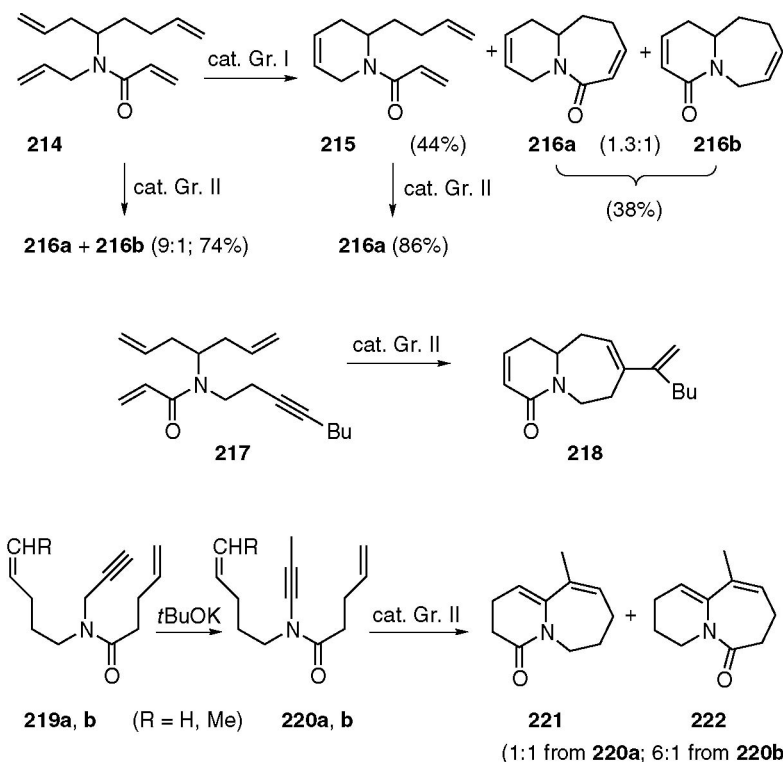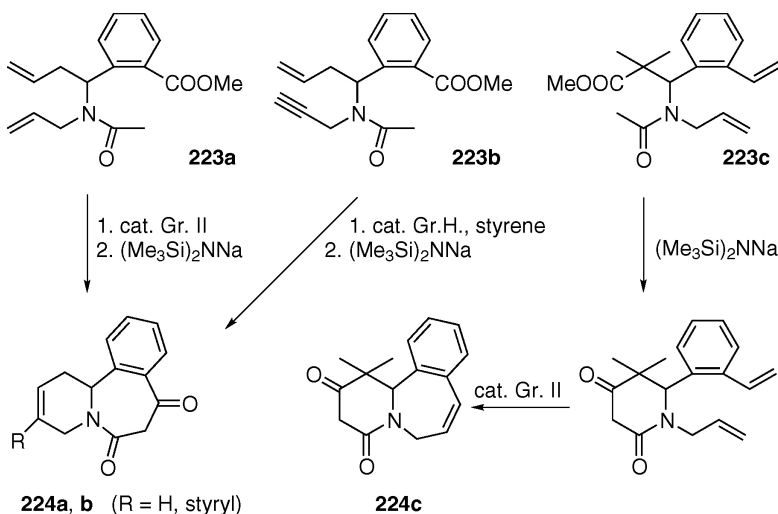
Scheme 52

from **240** hydrochloride in the presence of an alkylating agent and triethyl-amine, the products can be obtained in a single step. The reduction of precursor **240** yields tetrahydroisoquinoline **243** that reacts slowly with aromatic aldehydes to furnish, for example, diphenyl derivative **242a** in a low yield.

13-Methylene derivatives (e.g., **246**, Scheme 58) of the same ring system are synthesized from iminium salts (e.g., **245**, reacted *in situ*) by additive-enhanced palladium–indium catalytic three-component cascade methodo-logy, consisting in the reaction with allene and palladium salt, transme-tallation of a (π-allyl)palladium(II) species with indium, and regioselective 7-*endo-trig* cyclization to generate enamine **246** or analogs substituted in the A, B, and/or D rings (05CC3071). A similar reaction of 3-(3-furyl) pyridine and dihalide **244** yields **248**.

250-Type enaminones are generated by sequential bicyclization of β-phenylethyl phenylacetamides (e.g., **249**) in the presence of Lewis acid and oxalyl chloride that acts as a α-dicarbonyl transfer agent (00T993).

Scheme 53

2.6.2 By annulation onto the seven-membered ring

2.6.2.1 Alkylation, cycloaddition, and ring-closing metathesis (Scheme 59)

A surprising synthesis of 1,2-fused pyridinium salts (type **230**) is exemplified by the formation of derivative **252** from dihydrofuran **251** (83CL21). Amide **253** undergoes, in analogy with homoberbine syntheses, twofold cyclization to achieve enamine **254** (03WO84963).

The same framework is contained in enaminone **256**, which is the product of an aza-Diels–Alder reaction of morphanthridine **255** (made in five steps from anthraquinone) and Danishefsky's diene (07WO25938).

Tricyclic amine **259** forms by allylation and ring-closing metathesis from optically enriched precursor **258** that itself is the product of asymmetric RCM (03OL4899).

2.6.2.2 Pathways to homoberbines (Scheme 60)

Iminium salt **204c** with alkali gives smoothly the corresponding enamine that by cyclization (ring C) affords K-type homoberbine **260** and by subsequent protonation tetracyclic iminium salt **261** (95LA567). P-Type iminium salts **264a** and **b** are generated in the same way (89LA1).

2.6.3 By other approaches

Cyclic Reissert equivalent compound **265** yields, by transformation into intermediate **266** followed by sulfuryl chloride-mediated ring-opening rearrangement, L-type homoberbine enamide **267** (05T5037).
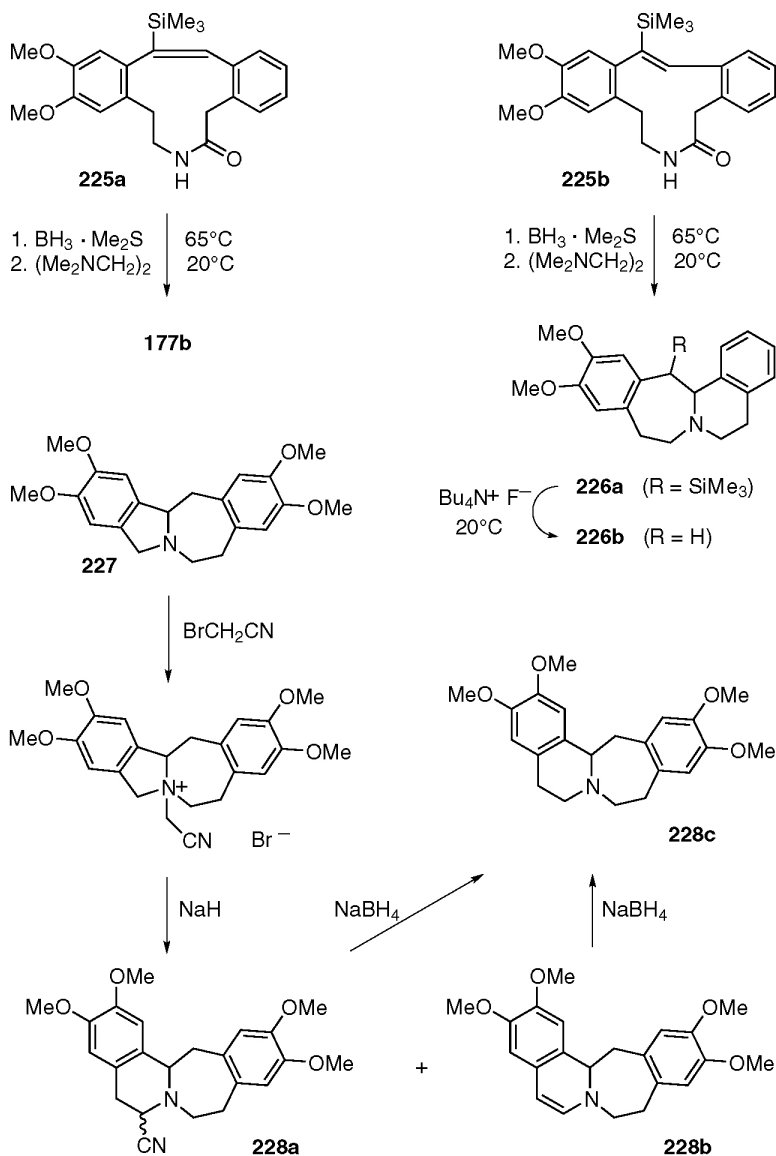
Scheme 54

Similar (partly isomeric) enamides **269a** and **b** and **270b** (Scheme 61) are generated from aminoalcohols **268a** and **b** by Pictet–Spengler reaction, oxazolidone ring formation by means of the phosgene equivalent, and ring rearrangement (84BF(2)317).
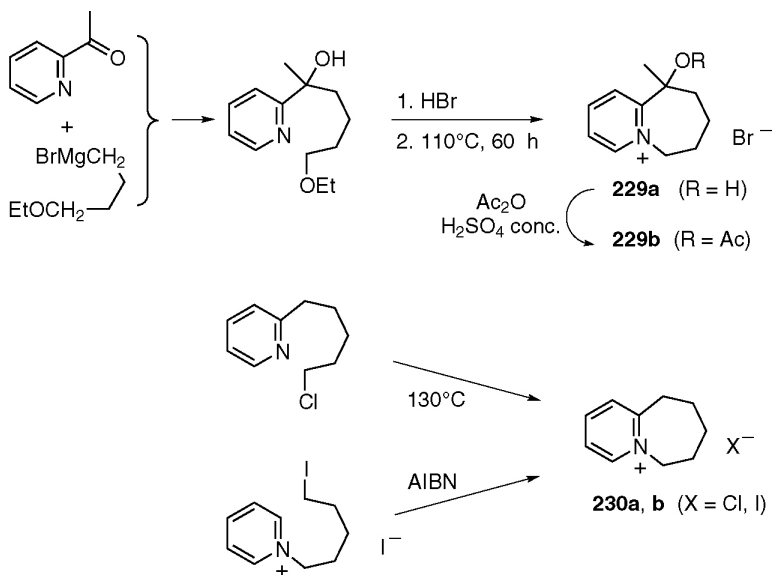
Scheme 55

Tetrahydro derivatives are formed as well by the dehydrogenation (see Section 4.2.4) of higher saturated analogs, such as homoberbines **173**, **177b**, and **202c**, and by the reduction (see Section 4.3) of higher unsaturated compounds, such as **307** and **308**.

2.7 Synthesis of dihydropyrido[1,2-a]azepine derivatives

2.7.1 By annulation onto the six-membered ring

2.7.1.1 *N*-Alkylation (Scheme 62)
The first approach to highly unsaturated bases led through dihydromorphanthridizinium salt **273a** to dihydropyridobenzazepine **274** (61TH1), which proved to be a red-colored, unstable pyridonemethide-type enamine (cf. 24CB522) and could be stabilized by the transformation to carboxanilide **275**.

2.7.1.2 Cycloaddition
Next, in chronological order, Acheson and his group, in his series "Addition reactions of heterocyclic compounds" (cf. 63AHC(1)125), extended the range of substrates to pyridine derivatives and initially believed to have found numerous pyridoazepines. The contents of six experimental articles (1968–1975), however, were for the most part revised
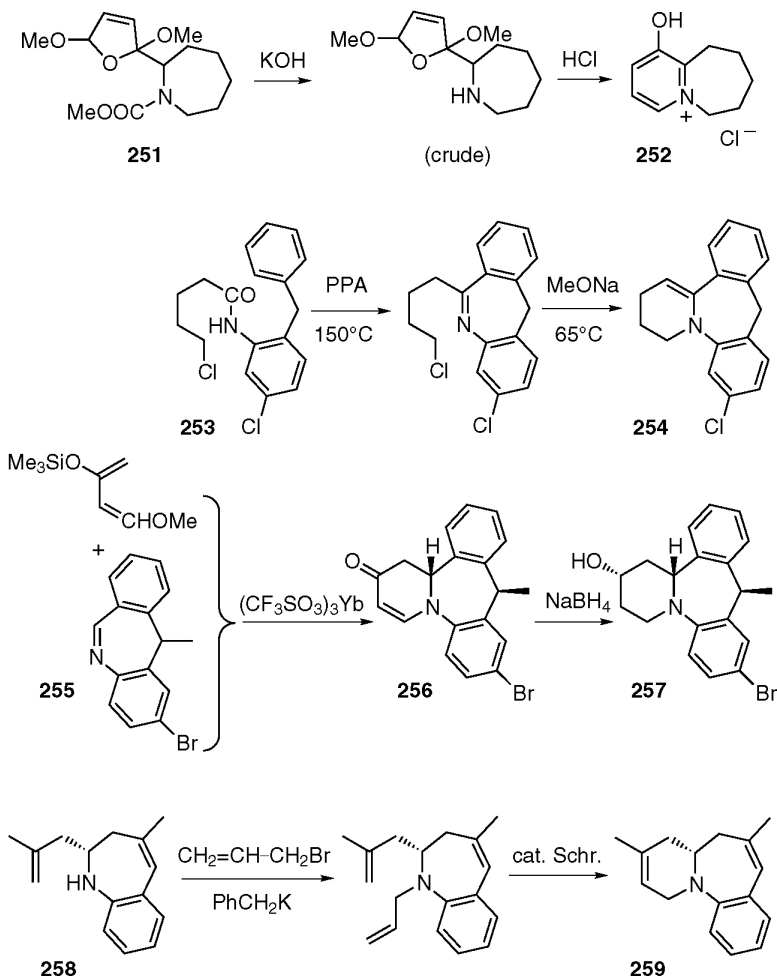
Scheme 56

from 1976 in a subsequent article (77J(P1)1924) and in reviews (76CHE837, 78AHC(23)263, p. 388ff). Most compounds initially considered to be pyridoazepines are, in fact, cyclobutaindolizine derivatives (cf. **279**).
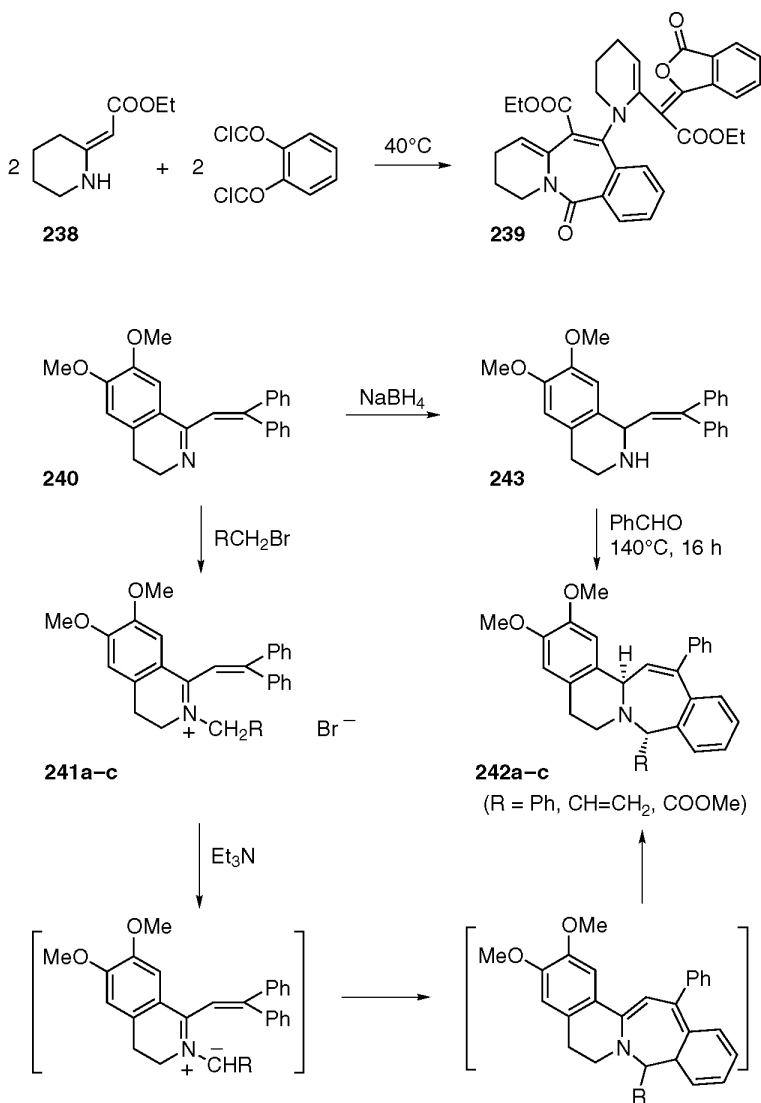
Scheme 57

(a) Among *reactions of pyridines* (Scheme 63), 2-hydroxymethylpyridine derivatives with dimethyl acetylenedicarboxylate (**276a**) indeed afford red-colored pyridoazepines **277c–e** as 1:2 adducts (79J(P1)584). The complicated reaction of dimethylpyrazine with the dicarboxylate, however, probably gives tricyclic **279** (77J(P1)1924) rather than originally proposed pyridoazepine **278** (68JC926).
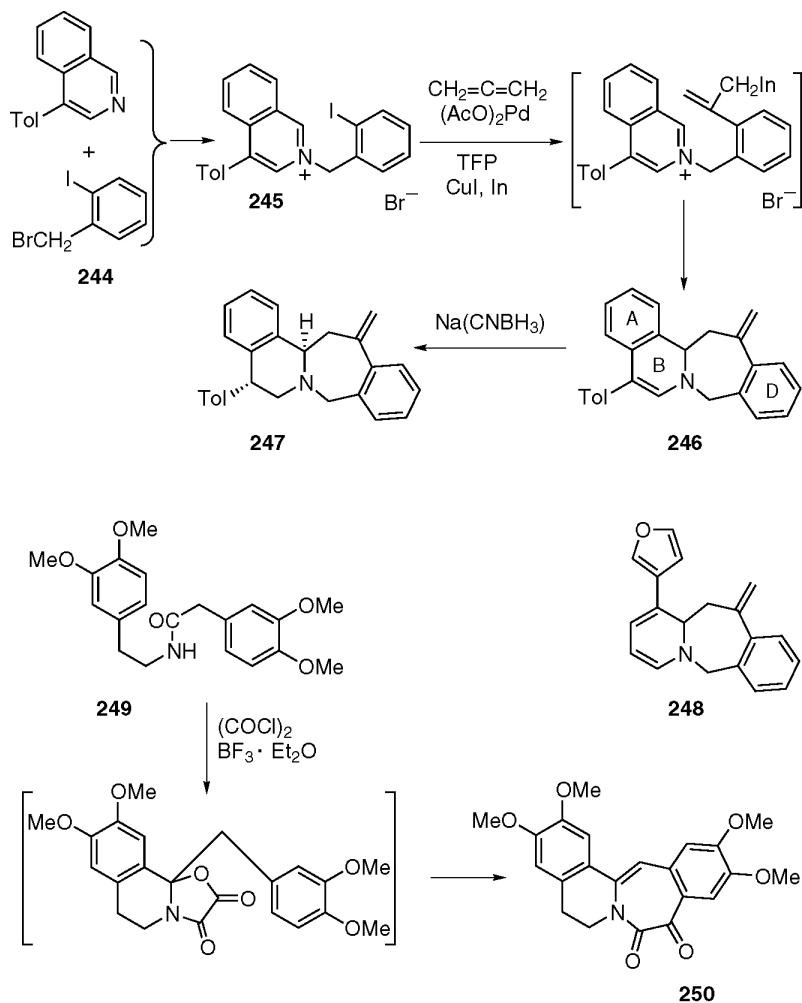
Scheme 58

(b) Among *reactions of quinolines* (Scheme 64) preliminary work that, for a long time, lacked final structural proof had been done by the groups of Diels, van Tamelen, and Crabtree with quinaldine [see 78AHC(23) 263, p. 394]. In Acheson's group, quinaldine and numerous derivatives with dimethyl ester **276a** each gave several, partly colored products, among them benzo-fused quinolizines and (initially erroneously suggested) pyridoazepines (68JC362, 68JC383, 71JC3291, 73J(P1)1338, 75J(P1)394) that were later recognized to be cyclobutaindolizines. The reactions are strongly solvent dependent.

Scheme 59

Thus, the main products from quinaldine in aprotic solvent acetonitrile are quinolizine **280** and indolizine **281a** (rather than pyridoazepine **282**); in protic solvent methanol only indolizine **281a** forms, but in both cases higher-fused products (1:3 and 1:4 adducts) are accompanying. Also the long-lasting discussion about the products obtained from 6-bromoquinaldine has been settled in favor of the two isomers **283** (76J(P1)692).

Contrarily, diethyl acetylenedicarboxylate (**276b**) with quinaldine gives far fewer isolable products than does the dimethyl ester; it affords no quinolizine but instead actually gives pyridoazepine **284** and cyclobutaindolizine **281b**.
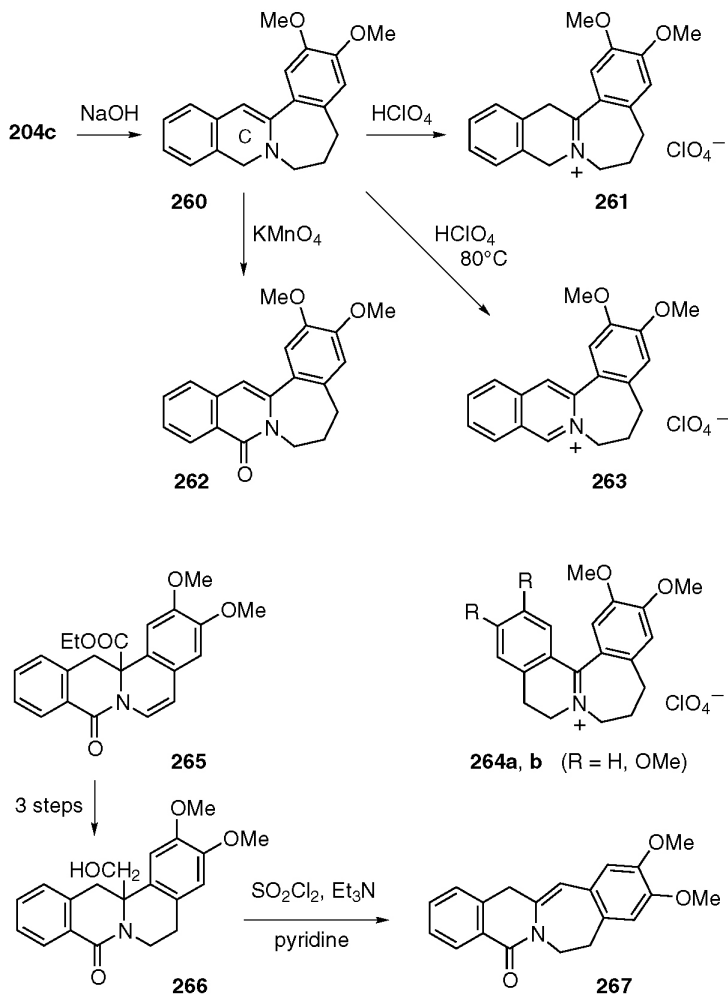
Scheme 60

(c) The *reaction of 6-methylphenanthridine* (Scheme 65) yields cyclobutaindolizine **285b** rather than pyridoazepine **285a** as first suggested (68JC362).

2.7.1.3 Cyclocondensation

A recent patent discloses the synthesis of quinobenzazepine **286a**, together with two isomers (11-carboxylic acid and quinophthalone dye **286b**) (10JAK143896).
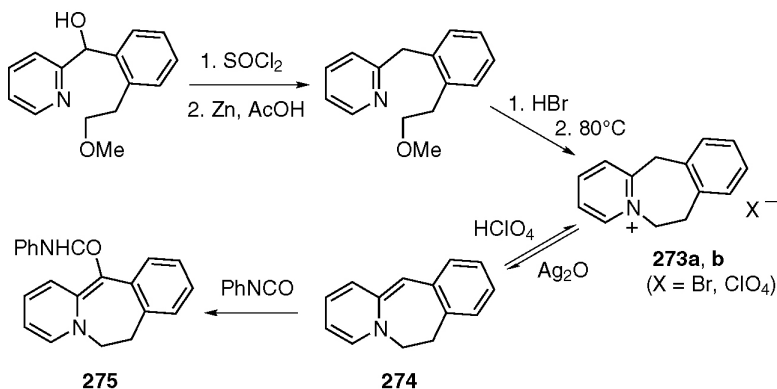
2.7.1.4 Ylide reactions (Scheme 66)

Later Ebersbach's group transformed pyridinium salts **287** and **289** by deprotonation and subsequent 1,7-electrocyclization of conjugated
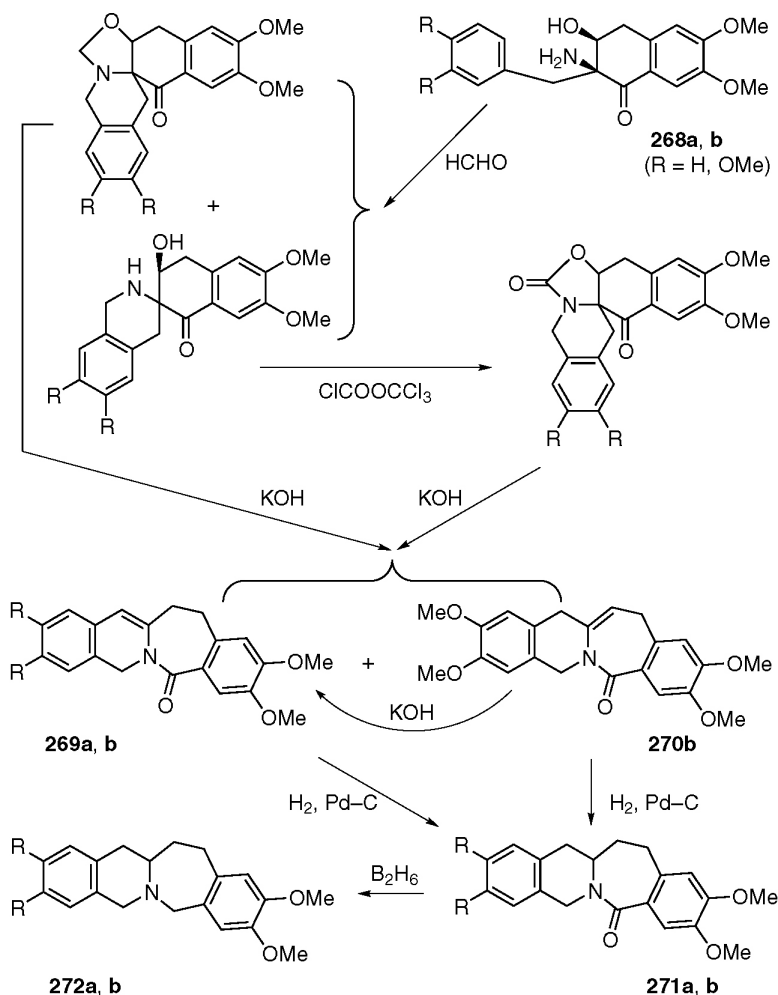
Scheme 61

pyridinium ylides (azomethine ylides) into heterobicyclic allenes that under oxidative conditions gave pyridoazepinones **288** and **290**, respectively (91HCA1095, cf. 04SOS(27)411, p. 462).

However, pentadienylpyridinium bromides (e.g., **291a–d**) upon deprotonation and 8π-electrocyclization [cf. 99AHC(73)97] afford dihydropyridoazepines, such as **292a–d** (97T14687). (R_F values are given.) The synthesis of derivatives **293a** and **b** serves to elucidate the stereochemical mode of the ring closure step; the results corroborate the predicted conrotatory manner. The C-10a bridgehead proton and the C-10 phenyl group are *trans*-disposed. There is no indication of the competitive

HO

1. SOCl$_2$

2. Zn, AcOH

OMe

N

OMe

N

1. HBr
2. 80°C

HClO$_4$

Ag$_2$O

273a, b
(X = Br, ClO$_4$)

X $^-$

N
+

PhNHCO

N

275

PhNCO

N

274

HClO$_4$

Scheme 62

CH$_2$OR

N

+ 2

COOMe

COOMe

276a

RO   COOMe

COOMe

N

MeOOC   COOMe

277c–e   (R = Me, Ac, COPh)

N
N

3 **276a**

3 **276a**

MeOOC   COOMe

MeOOC

COOMe

MeOOC   N

COOMe

278

COOMe

MeOOC

COOMe

MeOOC   N

MeOOC

279

COOMe
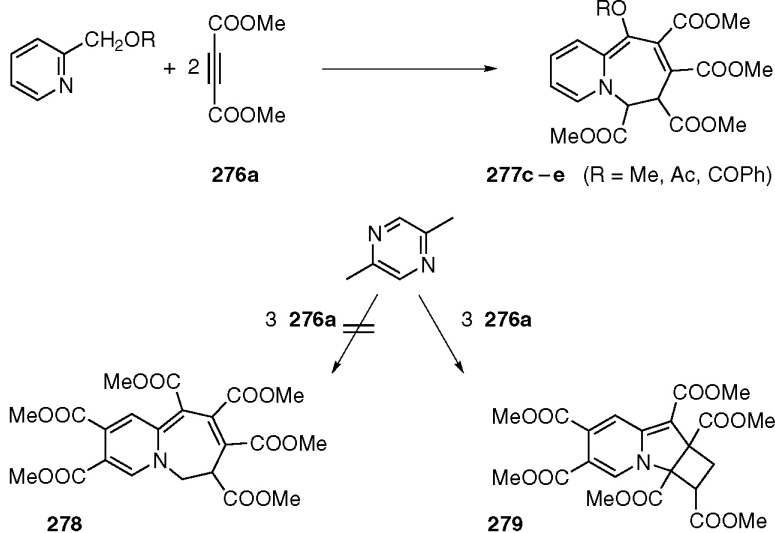
Scheme 63

formation of indolizines resulting from a 6π process; on the basis of quantum mechanical calculations on **294**-type derivatives a rationalization of the periselectivity of the electrocyclization process is given (00CEJ2063).

2.7.1.5 Allene reaction, cycloisomerization (Scheme 67)

The insertion of allenes in the palladium–carbon σ bond of cyclopalladated pyridine derivative **295** (cf. 00CRV3067) affords stable, isolable (η^3-allyl) palladium complexes (e.g., **296**) (03JOM(687)313). The ideally located imine unit when depalladated reacts selectively with the allyl functionality to yield methylene morphanthridizinium salts **297a–c**.
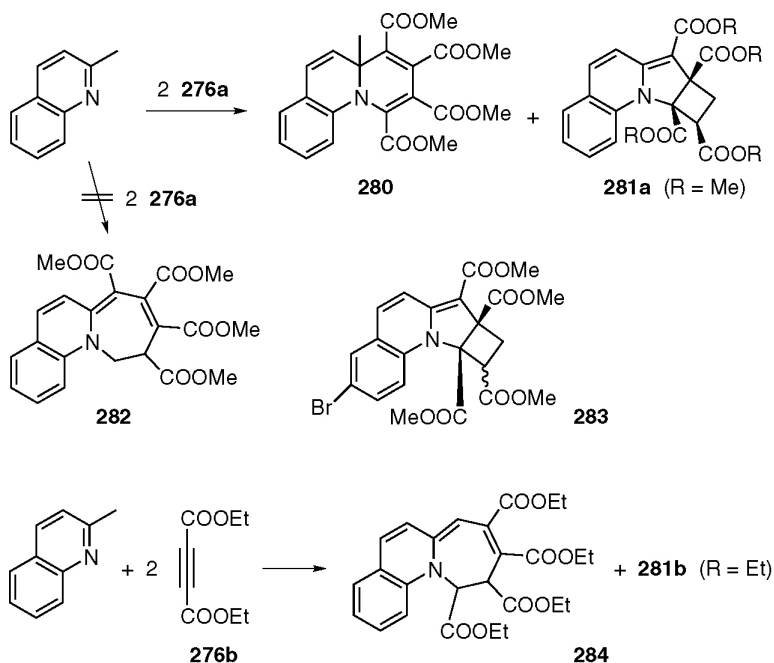
Scheme 64

Triyne **298** (obtained by Sonogashira coupling and bis-quaternization), in the course of helquat (i.e., diazoniahelicene) syntheses, undergoes [2+2 +2] cycloisomerization in the presence of Wilkinson's catalyst to yield helquat **299a** (09CEJ1072). From mono- and bis-isoquinoline precursors, two successive distinct pyridine-type nitrogen quaternizations followed by cycloaddition afford nonsymmetric [6] and [7] helquats, respectively, for instance, salt **299b** (10T3537).

2.7.1.6 Ring-closing metathesis
At high dilution ring-closing metathesis (Scheme 68), in its first application to cationic heteroaromatics, provides an access to pyridinium salts **300** and **301** (04OL4125).

2.7.2 By other approaches
Dihydropyridoazepines form by the dehydrogenation (see Section 4.2.4) of higher saturated analogs, such as dione **236a** or homoberbines **173**, **209b**, and **260**.

In the hands of Fozard and Jones (65JOC1523) bromination of pyridinium salt **303** (Scheme 69, upper part) yielded bromides **304a** and **b**. Acetylation of ketone **303** and monobromide **304a** led to enol esters **305** and **306**, respectively.
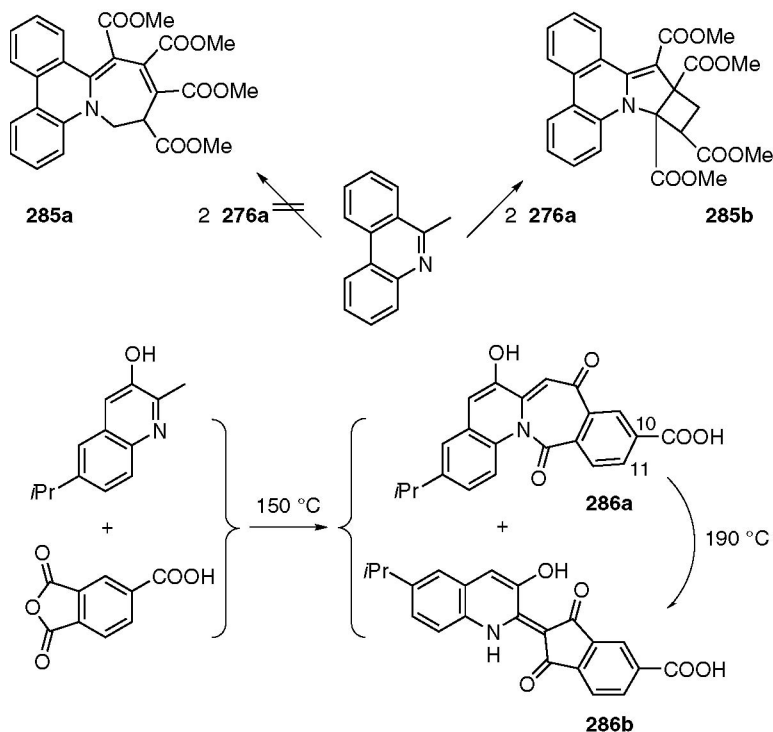
Scheme 65

2.8 Syntheses of pyrido[1,2-a]azepine derivatives

2.8.1 Pyrido[1,2-a]azepine bases

The challenging goal of synthesizing fully unsaturated pyrido[1,2-*a*]az-epines seemed to be reached when Fozard and Jones in the article just mentioned claimed the transformation of pyridinium salt **304b** through pyridoazepinium salts **307** and **308** (Scheme 69, lower part) to red pyri-doazepine **309** that might be stabilized by mesomerism including betaine structure **310**. The red compound, however, later had to be reformulated as monocyclic butadiene **311**, bicyclic **310** presumably having only transient existence (82JOC2792). Monobromo **307** in analogy gives butadiene **312**.

Finally Ebersbach's group succeeded in synthesizing the first (and, up to now, only known) authentic pyrido[1,2-*a*]azepine base **315** (Scheme 70) from their lactam **290** by thionation with Lawesson reagent (LR), methylation of thiolactam **313**, and deprotonation of sulfenium salt **314** (91HCA1095).

Another attempt had failed (61TH1): both propenyl- and allylpyridine with bromoacetone or phenacyl bromide, in the mode of three-carbon
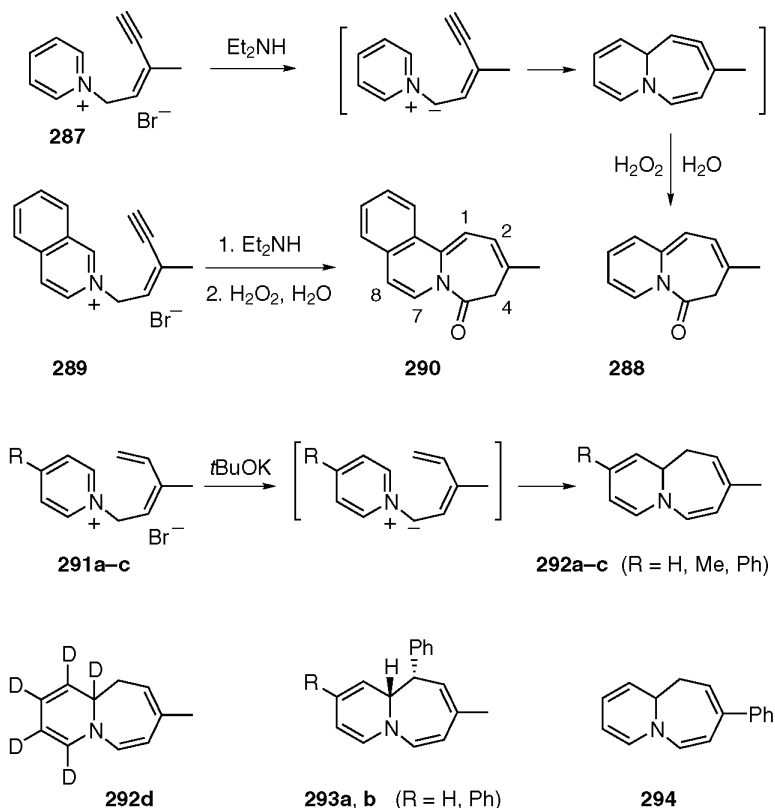
Scheme 66

tautomerism, gave quaternary salts **316a** and **b** that when cyclized, sur-prisingly, formally expelling HBr and acetaldehyde, afforded known indolizines **317a** and **b**, respectively.

2.8.2 Pyrido[1,2-a]azepinium salts

By contrast to the bases, the cationic species have long been known. In addition to Fozard and Jones' bicyclic salts already described (**307**, **308**), benzo-fused derivatives were synthesized in the context of the *aromatic cyclodehydration* series by Bradsher's group (Scheme 71). Different from the 2-propenylpyridinium salts **316** just mentioned, the cyclization of 2-benzylpyridinium **318** salts does not give indolizines unless under basic conditions; in the acidic medium *morphanthridizinium salts*, such as **319a** and **b**, are formed (59JA2547). This cyclization (after iodo-chloro metathesis) takes place in several days but in the case of the
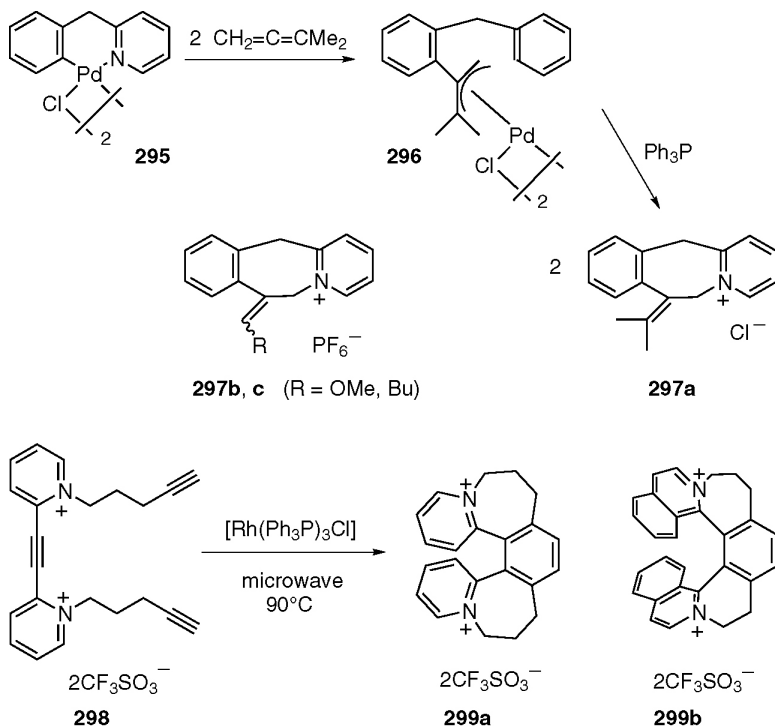
Scheme 67

9,10-dimethoxy derivative of salt **319a** only 90 min are necessary. The *N*-phenacyl analog of salt **318a**, however, does not react at all unless dimethoxylated in the benzyl moiety. Quaternization by chloroacetaldoxime opens the access to parent substance **320** (63JOC3205).

321-Type quaternary salts (nearly isomeric to **318**) cyclize to give small yields of *isomorphanthridizinium salts*, such as **322a** and **b** (61JOC3278).
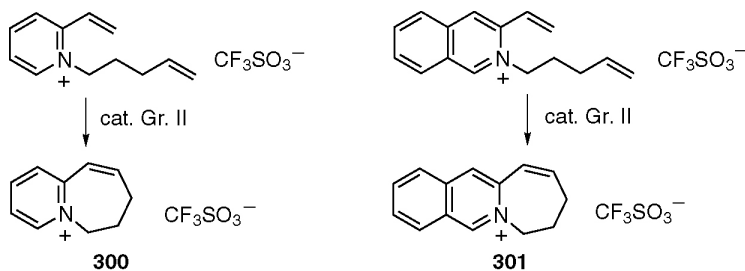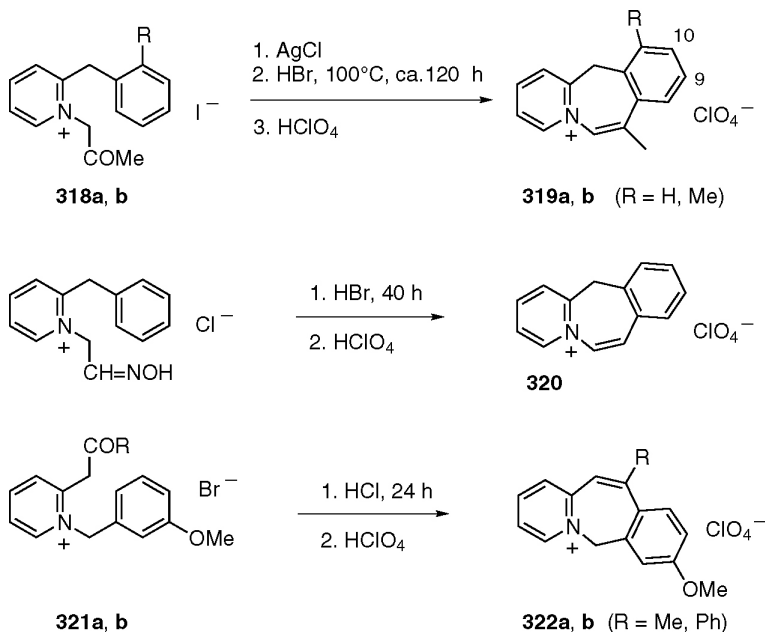

Scheme 68
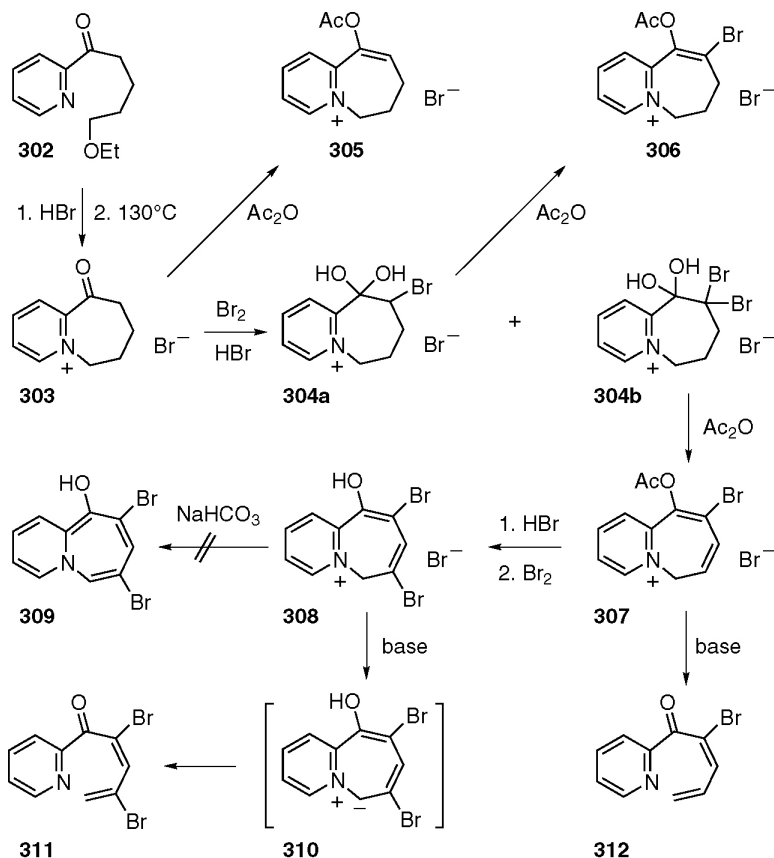
Scheme 69

Quaternary salts without any methoxy group do not cyclize at all, two ether groups enable performing the reaction in only 2 hours.

Morphanthridizinium salts also originate from six-membered palladocycle **323a** (Scheme 72) by alkyne insertion (87OM2043). After chloro-iodo metathesis, iodo-bridged complex **323b** reacts with diphenylacetylene to give a mixture of quaternary salts **324a** and **b**. Phenyl propiolate, on the other hand, converts precursor **323a** into an eight-membered ring containing complex **325a** that, after chloro-iodo metathesis, yields analogous salt **326** in a low yield. Therefore, both reactions may proceed by alkyne insertion into the palladium–carbon bond, accompanied by ring enlargement of the palladocycle, subsequent depalladation, and carbon–nitrogen bond formation.
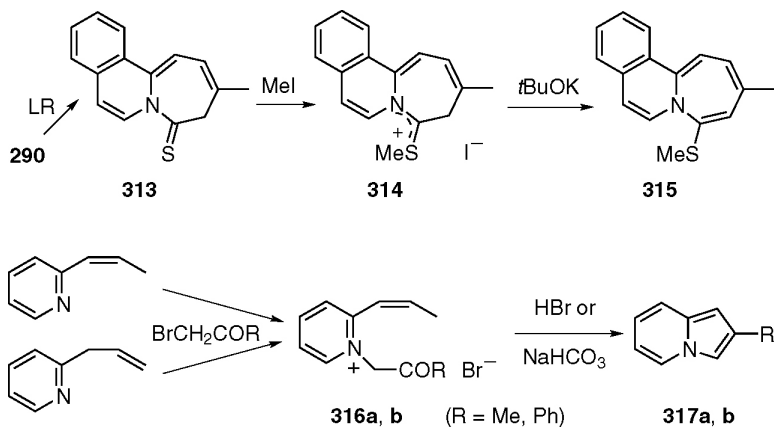
Scheme 70

Scheme 71

2.9 Summary of preparative data

2.9.1 Fused pyrido[1,2-a]azepines

Table 1 lists monobenzo- and dibenzo-fused compounds (including cationic species) that were synthesized by the methods given in Sections 2.4–2.8.
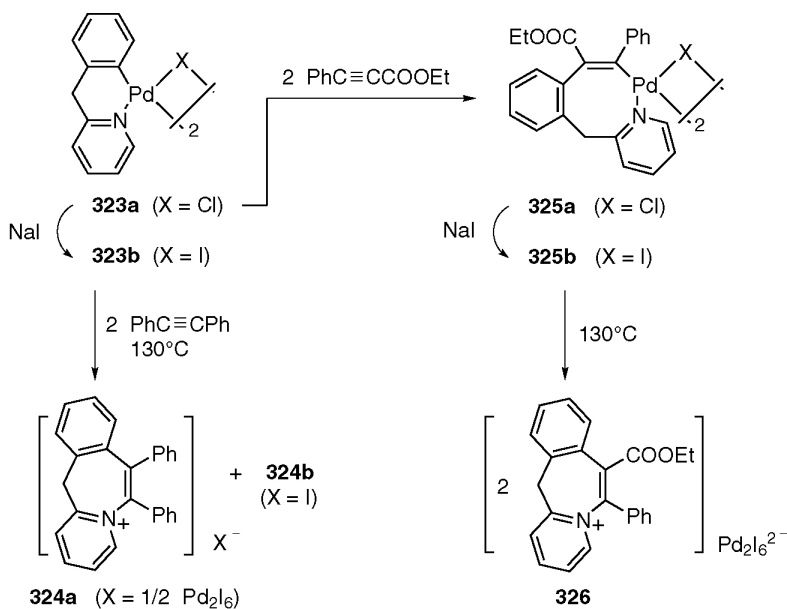
Scheme 72

Table 1. Fused pyrido[1,2-*a*]azepine syntheses reviewed in Sections 2.4–2.8

Ring system	Type or example	Other compounds
Azepino[1,2-*a*]quinoline	**4**	**91, 112b, 113b, 190, 232, 284**
Azepino[1,2-*b*]isoquinoline	**78b**	**88a–c, 148, 150a, 200, 236a, 301**
Azepino[2,1-*a*]isoquinoline	**315**	**137, 149, 290, 313, 314**
Pyrido[2,1-*a*][2]benzazepine	**5**	**79b, 81a, 84a, 102, 127, 131, 133, 224a–c**
Pyrido[2,1-*b*][3]benzazepine	**274**	**69, 297a–c, 319ab, 320, 324ab, 326**
Pyrido[1,2-*b*][2]benzazepine	**89b**	**71, 89ac, 116, 129, 239, 248, 322ab**
Pyrido[1,2-*a*][1]benzazepine	**109**	**78d, 259**
Azepino[1,2-*f*]phenanthridine	**233**	
Quino[1,2-*b*][2]benzazepine	**286a**	
Isoquino[3,2-*a*][2]benzazepine	**151K**	**202a–c, 260**
Isoquino[3,2-*b*][3]benzazepine	**151L**	**205ab, 267**
Isoquino[2,3-*b*][2]benzazepine	**210**	**213, 269ab, 270b**
Isoquino[1,2-*a*][2]benzazepine	**151P**	**179, 181, 182, 209ab, 264ab**
Isoquino[1,2-*b*][3]benzazepine	**151N**	**177ab, 178bc, 206, 226a, 228a–c, 250**
Isoquino[2,1-*b*][2]benzazepine	**6**	**155, 157ab, 160, 161, 163, 164, 167, 173, 174, 242a–c, 246**
Dibenzo[*c*,*f*]pyrido[1,2-*a*]azepine	**135**	**134, 254, 256**
"Helquat"	**299a**	**299b**

2.9.2 Scope and limitation of the syntheses

Ring homology is regarded as a classical criterion for the design of analogs of bioactive compounds (09CEJ4565). Many syntheses reviewed here can also be applied to nitrogen-bridgehead bicyclic structures beyond the limits of the pyrido[1,2-*a*]azepine chemistry. These reactions are sometimes specific to the pyridine or the azepine moiety but can be even more generally useful. With respect to these three types of syntheses, Table 2 lists the scope of application in terms of the respective 1-azabicyclo[*m.n*.0] alkanes **327a** (Scheme 73) involved and characterizes them by formula numbers of the synthesized substances that were described in Sections 2.3–2.7 and can serve as starting points for generalization.

An example of an intriguing ring-size dependency of the reaction pathway is that of the cyclization of vinylogous urethanes **328a–c** with cinnamaldehyde (08T883). Pyrrolidine- and azepane-based esters **328a** and **c**, respectively, give via aza-[3+3] annulation the expected

Table 2. Generalization of syntheses reviewed in Sections 2.3–2.7

Range of application within the [*m.n*.0] series		Synthesized [5.4.0] compounds
m	*n*	
2–5	4	**42**
3–5	4	**46, 49, 58** (from **57** or **111b**), **73, 78b** (from **78a** or **101**), **86/87, 94, 95b, 102, 104, 105, 123b, 124a, 148, 184, 189, 190** (from **183b** or **191b**), **196ab, 200, 252**
3, 5	4	**188c, 192a, 230b**
3–6	4	**65, 112b**
4–5	4	**37, 75, 77, 115, 137, 138, 144ab, 149, 187, 218, 229a**[a], **230a, 297, 299a, 301**
4–6	4	**299b, 300**
4–7	4	**95a, 98**
4–7, 11	4	**40b**
5–6	4	**109**
5	3–4	**29a, 67, 131, 134, 143, 206**
5	3–5	**129, 140**
5	4–5	**114, 181**
3–5	3–4	**21, 23, 32, 39a, 60, 63**
3–5	3–5	**85, 107**
3, 5	3–5	**128**
3–6	3–4	**31, 92, 109**
3–7, 11	3–4	**20** (from **53**)
4–5	3–4	**89**
4–5	3, 4, 6	**221/222**
4–5	4–5	**216**
4–6	2–4	**93**

[a] cf. 59JCS1686.
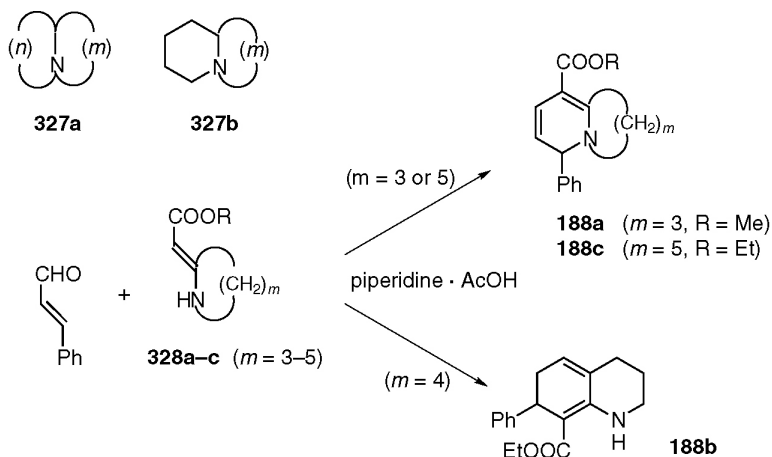
Scheme 73

nitrogen-bridgehead esters **188a** and **c** (cf. Section 2.5.2.1) whereas piper-idine-based ester **328b** undergoes a carba-[3+3] annulation to afford hexahydroquinoline **188b**.

Table 3. Ring-size dependency of annulation reactions

[5.4.0]-Type compound	Cyclization type	Synthesis parameters and results with [*m*.4.0]-type analogs (**327b**)	References
63	*N*-Alkylation	*m* = 3 or 4: Et$_3$N, 25°C	04JOC2128
		m = 5: *i*Pr$_2$NEt, 110°C	
124a (A)	*N*-Alkylation	*m* = 3 or 4: DBU	01JP11435
		m = 5: (Me$_3$Si)$_2$NK, 18-crown-6	
		m = 3/4/5: yield 95/88/46%	
229a	*N*-Alkylation	*m* = 4: 60°C	59JCS1686
		m = 5: 80°C (220 h) or 110°C (65 h)	61TH1
23	Dieckmann cyclization	*m* = 3 or 4: *t*BuOK	92BML1147
		m = 5: NaH (high dilution)	
73	Enamine cyclization	*m* = 4/5: yield 72/46%	92JA7292
75a	Enamine cyclization	*m* = 4/5: yield 72/32%	08T3464
78b (from **78a**)	Enamine cyclization	*m* = 3/4/5: yield 88/77/51%	04TL2855
39a-isomer (6,6-diester)	Iminium salt cyclization	*m* = 4: smooth reaction	79JOC4173
		m = 5: iminium ion does not cyclize	
138	C–C coupling	*m* = 4/5: yield 79/26%	07CEJ7443
85	Thermolysis	*m* = 3/4/5: yield 78/71/30%	83CJC2016
86a, **87a**	Electrolysis	*m* = 4/5: yield 58/14%	95AGE2007
92	RCM	*m* = 4/5/6: yield 91/84/50%	96T7251
300, 301	RCM	*m* = 5 or 6: high dilution (0.005 M)	04OL4125

2.9.3 Ring-size dependency of reaction conditions and results

Ring-size dependency that is less dramatic, than the example just mentioned, relates to conditions or yields of reactions leading to ring-homologous 1-aza-bicyclic substances. Table 3 lists a selection of products (already dealt with in Table 2) in the context of small ring-homologous series (**327b**) obtained by ring-closing on an existing six-membered ring. As known from other examples the formation of seven- and higher-membered rings is usually more difficult than that of five- and six-membered rings.

Sometimes, however, any ring-size dependency cannot be observed as in small ring-homologous series including iminium ion cyclization products **77a–c** (92T2081) and especially ring-closing metathesis products, such as **93** (99J(P1)1695), **94** (01JOM9056), **124b** (06OL951), or **95a** (04JOC7114). In the latter case, the yields of six-, seven-, eight-, and nine-membered ring-closing uniformly reach 95–97%.

On the other hand, annulation of a six-membered ring can also become significantly more difficult on increasing the ring size of the existing ring, for instance, with ring-homologous series including carbonylation products **78b** (from **101**) (06JOC5951) and **200** (08CL4987) and RCM product **115** (99SL1127).

3. STRUCTURE

3.1 X-ray diffraction

X-ray analysis (Table 4) mainly serves in determining molecular structures or stereochemical details. Thus, the final decision in favor of tetracyclic structure **283** was based on an X-ray determination (see Section 2.7.1.2).

Table 4. X-ray diffraction of pyrido[1,2-*a*]azepines

Ring system[a]	Formula[b]	References
Pyrido[1,2-*a*]azepine	**42b**	98T2529
	77a	92T2081
	347	04CEJ3286
Pyrido[2,1-*a*][2]benzazepine	**82a**·HCl	91JME511
	102	08OL4267
	353b·MeOH	76JOC2454
Pyrido[1,2-*b*][2]benzazepine	**239**	02T2821
Isoquino[3,2-*a*][2]benzazepine	**202c**	95LA567
Isoquino[1,2-*b*][3]benzazepine	**177b**	97LA447
Isoquino[2,1-*b*][2]benzazepine	**173**	94LA1135
	247[c]	05CC3071

[a] The structures can be gathered from the formulas (in following tables, too).
[b] For structures above **328** see below in Section 4 (in following tables, too).
[c] And dihydro-**248** (the enamine double bond was hydrogenated).

Table 5. ¹H-NMR chemical shifts of bicyclic pyrido[1,2-a]azepine derivatives

Structural type	Formula	δ (ppm)[a,b] in positions[c,d]										Solvent[e]	References[f]
		1	2	3	4	6	7	8	9	10	10a		
Iminium salt	60	3.00–3.14	1.81–1.99		4.15–4.25	3.94–4.04	2.00–2.11	1.81–1.99	1.68–1.80	3.00–3.14	–	C	03T3099
Enaminoallene	77a[g]	2.04/2.27	3.47	–	7.50	3.13/3.45	1.44–1.56/1.77	1.35/1.91	1.99/2.25	–	3.96	C	92T2081
Lactamester	98	⋯⋯1.60–2.50⋯⋯			–	3.27–3.35/ 4.61–4.80	5.63–5.73		1.60–2.50		–	C	99SL1127
Pyridone	123b	6.05	7.10–7.50	6.48	–	4.25–4.55	⋯⋯1.60–2.05⋯⋯		⋯⋯	2.69–3.00	–	C	86JOC2184
Dieneamine	128					6.08	4.97	2.85		5.40		C	85TL833
Hydroxypyridone	189	–	–	6.09	–	4.50	⋯⋯1.79⋯⋯		–	3.23	–	C	02T2821
Pyridinium salt	230b	7.95	8.42	7.87	8.86	4.80	⋯⋯1.78–1.97⋯⋯		⋯⋯	3.33	–	N	91T4077
Tetraester	277c	⋯⋯2.70–3.20⋯⋯		3.75	2.70–3.20	⋯⋯4.55⋯⋯		–	–	–	–	T	79J(P1)584
6-Oxo compounds	288	6.66	6.25	5.90	7.90	–	2.59	(2.04)	6.09	5.81	–	C	91HCA1095
	344b	6.66	6.25	5.90	7.90	–	2.55	(2.04)	6.09	5.81	–	C	93H(35)817
	345	6.73	6.33	6.43	–	–	2.58	(1.80)	6.13	6.09	–	C	
10,10a-Dihydro compounds	292a	5.43	5.85	4.81	6.19	6.23	4.88	(1.90)	5.64	2.19/2.49	3.74	C	97T14687
	292b	5.14	(1.74)	4.68	6.16	6.22	4.85	(1.88)	5.60	2.16/2.45	3.70	C	
	292d	–	–	–	–	6.25	4.89	(1.90)	5.66	2.19/2.49	–	C	
	293a	5.48	5.86	4.36	5.91	6.28	5.00	(2.01)	5.98	3.73	4.01	C	
	294	5.51	5.91	4.87	6.27	6.44	5.31	–	6.03	2.27/2.80	3.78	D₂O	00CE2063
Pyridoazepinium salt	308	⋯⋯ca. 8.0–8.9⋯⋯			9.0	5.4	–	7.15		–	–	D₂O	65JOC1523

[a] Figures in parentheses refer to methyl groups.

[b] A slash separates δ values of two H atoms in methylene groups (in following tables, too).

[c] The numbering is that of the unsaturated pyrido[1,2-a]azepine (1).

[d] The extension of a dotted line marks those columns the data are relating to (in following tables, too).

[e] Solvents: C, CDCl₃; N, CD₃CN; T, CCl₄.

[f] Immediately successive identical references are not repeated (in following tables, too).

[g] δ values before and behind the slash have been assigned to axial and equatorial H atoms, respectively.

Table 6. ^{1}H-NMR chemical shifts of azepino[1,2-a] isoquinoline heterorings (91HCA1095)

Substitution	Formula	δ (ppm)[a] in positions[b,c]							Solvent
		8	7	5	4	3	2	1	
3-Me-5-oxo	**290**	6.24	7.77	–	2.4–3.3	(2.10)	6.17	6.37	$CDCl_3$
3-Me-5-thioxo	**313**	6.50	8.66	–	2.48/3.93	(2.08)	6.16	6.62	$CDCl_3$
3-Me-5-SMe, iodide	**314**	8.61	9.68	(2.79)	4.70	(2.20)	8.44	9.18	DMSO-d_6
3-Me-5-SMe	**315**	5.85	7.21	(1.84)	4.88	(1.74)	5.95	5.84	C_6D_6

[a] Figures in parentheses refer to methyl groups.
[b] For numbering see formula **290**.
[c] This range of positions corresponds to that of positions 3, 4, 6, 7, 8, 9, 10 in bicyclic pyrido [1,2-a]azepine (**1**).

3.2 Molecular spectra

3.2.1 ^{1}H-NMR spectra
^{1}H-NMR chemical shifts of the heterocyclic rings of selected substances are listed in Table 5 (bicyclic compounds), Table 6 (azepino[2,1-a]isoqui-nolines), Table 7 (several pyridobenzazepines), and Table 8 (several homo-berbine-type isoquinobenzazepines).

Shift assignment has also been reported with respect to bicyclic com-pounds **37** (09TA1217), **93** (99J(P1)1695), **95b** (10OBC2639), and **115** (99SL1127), to azepino-[1,2-b]isoquinolines **88a–c** (04EJO3611), to homo-berbines **157a** (87CJC2356), **179**-derivatives (88LA1099), **205a** and **b** (97H (45)2137), and **202c**, **260–263**, and (see Scheme 79) **351** (95LA567), to dibenzo[c,f]pyridoazepine **135** (01H(55)1519) and helquat **299b** (10T3537) and additionally to hydrochlorides of homoberbines **173** (94LA1135), **177a** and **b** (97LA447), and **205b** (97H(45)2137) and to **209a** hydrochloride and **209b** hydroperchlorate, which exchange their NH^+ protons in the presence of deuterium oxide (87LA639). The hydrogen of the ring junction (C-7) appears as a quadruplet between 3.5 and 4 ppm (88H(27)133).

^{1}H-NMR spectra served, for instance, in the structural elucidation of alkaloids astrocasine (**8**) and astrocasidine (**9d**) (65TL1761, 72AQ769), in the confirmation of α-pyridone structures **196a** and **b** (99T14611), in distinguishing isomeric enaminones **269** and **270b** (84BF(2)317), and in corroborating the structures of maximally unsaturated base **315** (91HCA1095) and both the deutero derivatives **344a** and **b** (see Scheme 78) (93H(35)817).

^{1}H-NMR spectra have been applied extensively to stereochemical questions, for example, with bicyclic stereoisomers **42a** and **b** (88H(27) 133) and **331a** and **b** (Scheme 75) (76JPS1389), with highly unsaturated

Table 7. ¹H-NMR chemical shifts of pyridobenzazepine heterorings (in CDCl₃)

Pyridobenzazepine type	Formula	δ (ppm) in positions[a]									References
		1	2	3	4	6	7	11	12	12a or b	
P.[2,1-a][2]b.a	**131**	.......0.86–1.96.........			2.19–2.25/	3.05	6.49			3.05(b)	99J(P1)2605
P.[1,2-b][2]b.a	**90a**		..1.56–1.76...	1.91–2.12	2.29–2.39	–	3.87/5.30	3.83–3.89	1.56–1.76	3.26–3.33(a)	02S87
	116				3.05/4.27	–		–	2.55/3.29	4.23(a)	85J(P1)2075
	129	......1.4–2.1.......				3.31/3.83	–	–	5.78	2.73(a)	97JOC7744

[a] For numbering see formulas **131** and **129**, respectively.

Table 8. ^{1}H-NMR chemical shifts of isoquinobenzazepine heterorings

Isoquinobenzazepine type	Formula	δ (ppm) in positions[a]								Solvent[b]	References
		5	6	8	9	10	13	14	14a or b		
Is.[1,2-a][2]b.a	179	2.76–3.03	2.64–2.72 / ......2.76–3.03.......	3.01–3.10 / ......2.76–3.03.......	1.85–2.00	3.32–3.37 / 2.76–3.03			5.35(b)	C	99PHA658 03H(60)887
	209b	........2.60–3.35........	........2.60–3.35........		1.65–1.95	2.60–3.35			5.12(b)	C	
	264a	3.14/3.46	4.12/4.39	3.04–3.07	2.3–2.5 / ......2.6–2.9........	.2.6–2.9........			–	N	89LA1
	350	8.31	8.45	4.22/4.61	2.6–2.8 / ......2.3–2.6........	2.8–2.9 / .2.3–2.6........			–	N	
Is.[1,2-b][3]b.a	177a[c]	3.06/2.88	2.77/3.34	2.96/3.29	3.41/2.68			3.63/2.96	3.92(a)	C	97LA447
	206	2.85	3.61/4.03	–	3.44/4.50			3.20/3.27	5.43(a)	C	09T351
	250	3.12	4.62	–	–			7.04	–	S	00T993
	349	3.12	4.17	4.62	3.31			4.81	–	S	97LA447
Is.[2,1-b][2]b.a	173[c]	2.99/2.50	2.50–2.71	4.47/3.96			3.15–3.25/2.83	1.89–1.98	4.20(a)	C	94LA1135
	242a	2.70	3.02/3.08	5.17				6.63	5.50(a)	C	05S2039
	348a	3.10	4.16	5.41			3.28	3.84	–	S	94LA1135
	348b	8.15	8.70	6.10			3.36	4.28	–	S	

[a] For numbering see formulas 179, 177a, and 173, respectively.
[b] Solvents: C, CDCl$_3$; N, CD$_3$CN; S, DMSO-d$_6$.
[c] δ values before and behind the slash have been assigned to axial and equatorial H atoms, respectively.

compounds **293a** and **b** (97T14687), with azepino- [1,2-*b*]isoquinolines **88a–c** (04EJO3611) as well as pyrido[2,1-*a*][2]benzazepines **403a** and **b** and **404a** and **b** (Scheme 89) (90TL815). The *Nuclear Overhauser Effect* (NOE) often serves to confirm the configurations, for instance, of **150a** and **376** (Schemes 37 and 85) and the respective stereoisomers (08TL5141) and of isomers **368a** and **b** (Scheme 84) (07T8267).

On the basis of ^{1}H-NMR data the conformation of bicyclic ketone **23b** (72OMR259), carbinol **24** (71JHC7), and azasugar **37** (09TA1217) has been determined. Data reveal some conformational mobility of the bicyclic systems of highly unsaturated **288** and **290** (91HCA1095), **292a** (97T14687), and **294** (00CEJ2063).

Special challenges of stereochemical assignment and conformational analysis with homoberbines were solved, for example, in the cases of iso-quinobenzazepines **169** (71T1363), **173** (94LA1135), **177a** and **b** (97LA447), **202c** (95LA567), **205a** and **b** (97H(45)2137), and **209b** (89LA1).

3.2.2 ^{13}C-NMR spectra

^{13}C-NMR chemical shifts of the heterocyclic rings of selected bicyclic compounds and of homoberbine-type isoquinobenzazepines (including the alkaloid saulatine, **11**) are listed in Tables 9 and 10, respectively. Shifts of α-olefinic and (at higher field) β-olefinic carbon atoms of enamines **77a**, **288**, and **292–294** and of the iminium group carbon atom in bicyclic salt **60** are found in the respective regions reported in the literature to be typical of such compounds (82T1975, p. 1986).

Shift assignment has also been published in respect of benzo deriva-tives, such as **88a–c** (04EJO3611), **90a** (02S87), and maximally unsaturated substance **315** (91HCA1095), of homoberbines **205a** and **b** (97H(45)2137), **202c**, **260–263**, and **351** (95LA567) including derivatives of **179** (88LA1099), and of helquat **209b** (10T3537).

3.2.3 ^{19}F-NMR spectra

The ^{19}F-NMR spectrum was helpful in determining the structure of per-fluoro compound **54** (88JFC(38)303).

3.2.4 Electronic spectra

Electronic spectral data for selected pyridoazepine bases and their salts can be found in Tables 11 and 12, respectively. Data have additionally been reported with reference to cyclic diimide **32** (64CB1548), to homoberbines **157a** and **b** and **158** (69HCA1228) as well as **160** and **161** (69JC874), and to hydroperchlorates, for instance, of homoberbine **209b** (87LA639).

The UV maximum (215 nm) of β,γ-unsaturated amine **25** (71JHC7) enables differentiating it from an isomeric enamine (α,β-unsaturated

amine) from which a maximum at about 224–228 nm should be expected (cf. 63JCE194).

Pyridonemethide-type enamines tend to extend their absorption into the visible region; they are partly deeply colored substances exhibiting distinct visible maxima (see Table 11). Among further enamines there are yellow-colored conjugated pyridonemethides **313** and **314** (91HCA1095) and red-colored conjugated enamines (nonpyridonemethide type), for instance, **292a**, **b**, and **d** and **293a** and **b** (97T14687) as well as **294** (00CEJ2063). Pyridoazepinone **288** absorbs at surprisingly higher wavelengths than its benzo-fused analog **290** (91HCA1095).

3.2.5 Infrared spectra

Some relevant IR bands of selected compounds are listed in Table 13. Detailed band assignment is available in the case of chiral substances **88a–c** (04EJO3611). Characteristic dialkyllactam vibration between 1660 and 1625 cm^{-1} is found in dihydroastrocasine (**9a**) (65TL1761) and fused pyridones **196a** and **b** (99T14611) while cyclic diimide **32** exhibits carbonyl bands at 1729 and 1656 cm^{-1} (64CB1548).

The conversion of a simple enamine to its salt is accompanied by a shift of the double bond and accordingly by an infrared shift from about 1650 cm^{-1} (C=C stretching region) to about 1680 cm^{-1} (C=N stretching region), which may be used in the identification of enamines (63JCE194, 82T1975, p. 1984). A similar shift (from 1600 to 1630 cm^{-1}) is observed with the much more complex homoberbine enamine **260** and perchlorate **261** (95LA567). The C=N$^+$ bands of iminium salts **60** (03T3099) as well as **264a** and **350** (see Scheme 79) (89LA1) are found at 1675, 1610, and 1620 cm^{-1}, respectively, the NH$^+$ band of simple **209b** hydroperchlorate (87LA639) at 2700–2500 cm^{-1}.

The presence of *Bohlmann bands* (marked bands in the 2800–2600 cm^{-1} region) in the IR spectra of saturated 1-azabicycloalkane moieties is a reliable indication of the presence of *trans*-fused ring conformations, for instance, with ketones **15** (71JHC7) and **23b** (72OMR259), hydroxy compound **331b** (see Scheme 75) (76JPS1389), and homoberbines **177a** and **b** (97LA447) and **205a** and **b** (97H(45)2137). By contrast, the absence of Bohlmann bands in homoberbines **169**, **171**, and **175** (71T1363), **173** (94LA1135), and **202c** (95LA567) indicates *cis*-conformation.

In carbinol **24** bands at 3600 and 3440 cm^{-1} provide evidence of an intramolecularly hydrogen-bonded hydroxyl group (71JHC7).

3.2.6 Mass spectra

Mass spectrometric fragmentation of substituents and rings are presented in Table 14. Among further examples, enamine **184a** shows (M$^+$ − nitrophenyl) as the base peak, a behavior typical of 1,4-dihydropyridines (77LA1888). Tetrabrominated lactam **347** (see Scheme 78) gives a

Table 9. ^{13}C-NMR chemical shifts of bicyclic pyrido[1,2-*a*]azepine derivatives (in CDCl$_3$)

Structural type	Formula	δ (ppm) in positions										References
		1	2	3	4	6	7	8	9	10	10a	
Iminium salt	**60**		28.8	23.9	59.7	55.6	20.9	21.5		37.4	193.6	03T3099
Enaminoallene	**77a**	31.1^a	37.0	104.7	146.9	55.8	29.0^b	29.6^b	31.7^a	93.3	57.2	92T2081
6-Oxo compound	**288**	127.2	121.8	108.1	128.1	162.0	42.7	129.1	121.4	110.1	136.1	91HCA1095
10,10a-Dihydro	**292a**	120.2	121.6	96.0	131.4	132.7	105.6	132.9	126.4	43.7	59.5	97T14687
compounds	**292b**	117.1	128.2	99.5	131.0	132.7	105.3	132.8	126.1	43.7	59.5	
	292c	117.9	132.9	96.8	132.1	132.3	106.0	132.4	125.6	43.6	59.6	
	293a	122.0	119.8	96.5	132.0	133.1	105.9	133.9	126.3	59.4	62.2	
	294	121.9	120.4	96.5	131.3	128.2	103.6	144.5	133.9	44.4	59.7	00CEJ2063

Values of the superscript letters (a and b) can be interchanged.

Table 10. ^{13}C-NMR chemical shifts of isoquinobenzazepine heterorings

Isoquinobenzazepine type	Formula	δ (ppm) in positions[a,b]										Solvent[c]	References
		14b or 14c(*)	4a	5	6	8	8a or 9(*)	9a, 10(*), or 12a(°)	10a, 13(*), or 13a(°)	14 or 14a(*)	14a or 14b(*)		
Is.[1,2-a][2]b.a.	**179**	136.0*	141.6	29.3	48.0	58.1	25.8*	33.8*	136.8	136.0*	63.1*	C	99PHA658
	264a	127.9*	140.3	26.4	53.2	58.4	34.8*	29.3*	138.0	121.2*	175.0*	N	89LA1
	350	128.4*	135.1	125.9	136.1	59.2	34.1*	28.8*	139.7	120.6*	159.7*	N	
Is.[1,2-b][3]b.a.	**11**	126.0^d	124.2^d	32.8	168.9	42.5	32.0*	128.7^e	132.8$^{°e}$	198.2	66.5	C	84JNP539
	177a	134.7	139.4	29.8	48.5	57.3	34.9*	142.1	141.2°	43.7	63.4	S	97LA447
	349	128.8	117.7	25.1	50.5	54.1	28.3*	133.3	135.6°	34.3	175.0	S	
Is.[2,1-b][2]b.a	**173**	125.7	132.0	29.0	42.6	60.5	138.5	142.2°	35.0*	31.2	65.3	C	94LA1135
	348a	118.0	130.2	25.2	51.5	59.0	133.4	136.6°	26.9*	27.3	176.5	S	
	348b	122.5		121.9	133.9	60.2	135.6	136.3°	25.0*	28.7	157.0	S	

Values of the superscript letters (d and e) can be interchanged.

[a] For numbering see formulas **179**, **177a**, and **173**, respectively.

[b] This range of positions corresponds to that of positions 1–10a in bicyclic pyridol[1,2-a]azepine (**1**).

[c] Solvents: C, CDCl$_3$; N, CD$_3$CN; S, DMSO-d$_6$.

Table 11. UV–vis maxima of pyrido[1,2-*a*]azepine bases

Structural type	Formula	λ_{max} in nm (log ε)	Color	Solvent[a]	References
α-Pyridone	196a	272 (4.04), 312 (3.66)		M	99T14611
	199	220 (4.18), 277 (3.96), 315 (3.96)		E	85JA5817
α-Pyridonemethide	275	246 (4.27), 350 (3.90), 425 (3.48), 445 sh	Pink	M	61TH1
	277c	236 (3.86), 252 (3.90), 405 (4.07), 505 (4.16)	Pink	M	79J(P1)584
	277d	254 (3.94), 384 sh, 394 (4.10), 489 (4.20)	Scarlet	M	
	277e	235 (4.40), 370 sh, 396 (4.11), 490 (4.19)	Red	M	
	288	240 (4.10), 315 (3.88), 370 (3.66)	Yellow	A	91HCA1095
Isoquinolonemethide	290	222 (3.35), 275 (3.52), 340 (3.97)		A	
	315	218 (4.40), 268 (4.23), 351 (3.78), 450 (3.78)	Dark red	CH	
α-Quinolonemethide	232	203 (4.45), 219 (4.41), 270 (4.41), 324 (4.01), 340 (4.01)		M	81MI1
Isoquinol[1,2-*b*][3]benzazepine	11	229 (4.40), 269 (4.04), 294 (3.94)		E	84JNP539
	250	242 (3.67), 288 (4.00), 340 (3.64), 380 (3.26)	Dark yellow	E	00T993
Isoquinol[2,1-*b*][2]benzazepine	155	210 (4.34), 225 sh, 282 (3.75)		E	71T1363
	167	228 (4.05), 280 (3.63)		E	
	169	281 (3.61), 284 (3.62)		E	
	170	227 (4.14), 281 (3.67)		E	
	171	230 sh, 281 (3.66), 285 (3.66)		E	
	175	212 (4.25), 282 (3.59), 286 (3.59)		E	

[a] Solvents: A, acetonitrile; CH, cyclohexane; E, ethanol; M, methanol.

Table 12. UV maxima of pyrido[1,2-*a*]azepinium salts

Ring system (cation)	Formula	λ_{max} in nm (log ε)			Solvent[a]	References
Pyridoazepinium	**230b**	218 (4.35)	268 (3.88)		E	91T4077
	305	242 (3.88)	300 (4.07)		W	65JOC1523
	307	244 (4.02)	317 (4.07)		W	
	308	258 (3.98)	258 (3.98)	410 (3.74)	W	
Morphanthridinium	**319b**	229 (4.19)	275 (3.72)	315 (3.81)	E	59JA2547
	320	225 sh	282 (3.69)	318 (3.83)	E	63JOC3205
Isomorphanthridinium	**322a**	231 (4.21)	275 (4.05)	363 (3.96)	E	61JOC3278
	322b	244 (4.07)	288 (4.01)		E	
Isoquinol[1,2-*a*][2]benzazepinium	**264a**	230 (4.02)	272 (4.12)	292 (4.11)	388 (3.79)	E	81LA1
	350	237 (4.60)	271 (3.97)	347 (3.69)	380 (3.84)	E	

[a] Solvents: E, ethanol; W, water.

Table 13. IR bands of pyrido[1,2-a]azepines

Structural type	Formula	Bands						In[a]	References
		=CH	CH	CO	CONR$_2$	C=C	C=N$^+$		
Ketolactame	**22**			1720	1645			P	62CPB366
	116			2950 1680	1626			K	85J(P1)2025
Enamine	**77a**							F	92T2081
	292a	3030 690	2856	1724		1640 1595		T	97T14687
	293a	3025 695				1640 1600		T	
Homoberbine (quaternary salt)	**263**		2960				1640	K	95LA567
	351		2950				1650	K	

^{a} F, film; K, KBr; P, capillary; T, CCl$_4$.

Table 14. MS fragmentation of pyrido[1,2-a]azepines

Structural type	Formula	Selected assigned fragment ions (I_{rel} in %)	References
Fluoroamine	**54**	M-C_8F_{15}N (50), M-C_9F_{16}N (57)	88JFC(38)303
Enamine	**77a**	M-CH_3 (1), M-OCH_3 (6), M-$COOCH_3$ (93)	92T2081
	292b	C_6H_9N (100), C_5H_6N (35)	97T14687
	293a	M-C_5H_5N (100), C_5H_5NH (54)	
	293b	M-2 C_6H_5 (100), M-$C_6H_5C_5H_5$N (32)	
	294	M-C_5H_5N (100), C_5H_6N (54)	00CEJ2063
	315	M-CH_3 (100), M-SCH_3 (23)	91HCA1095
Benzo-fused	**88b**	$C_{17}H_{22}$NO (100), $C_{10}H_{12}$N (27), C_9H_8N (22), C_9H_7N (8), C_4H_7N (8)	04EJO3611
	127	M-C_2H_4 (39), M-C_4H_8 (5), M-C_6H_5 (7),$C_{10}H_{10}$ (11)	05EJO2715
Astrocasine	**8**, **9a**, **9d**	C_6H_{12}N (N-methylpiperidyl) (100)	65TL1761, 72AQ769

pattern of five different (M$^+$ + H) peaks corresponding to different bromine isotope compositions (04CEJ3286). The mass spectrum of pyridinium salt **230a** indicates a dimeric structure (99M783).

The fragmentation of homoberbines **171** (71T1363) and **202b** and **c** (95LA567) is depicted in Scheme 74. **202**-Type compounds are mainly fragmented by a retro-Diels–Alder cleavage of the C ring. The most intense fragment observed in the mass spectrum of derivative **202b** is attributed to radical cation **329**, mesomerism-stabilized by two methoxy groups. Analog **202c**, however, that lacks methoxy groups on the D ring gives a much smaller band of fragment **329**. In this case the positive charge remains predominantly at benzazepine moiety **330**.

3.3 Stability and aromaticity

A number of pyrido[1,2-a]azepines fit with the pattern of decreasing stability on increasing the unsaturation. Among tetrahydro derivatives, only enamines astrocasidine (**9d**) and homoberbine **260** have been described to be sensitive to autoxidation (72AQ769, 95LA567). Nearly all the dihydro compounds, however, that is, enamines **292**, **293**, and **294** and other derivatives, undergo decomposition during workup and on longer standing (97T14687, 00CEJ2063). Pyridonemethide **274** can be sublimed *in vacuo* but in air it begins to turn brown after 10 min. The carboxanilide thereof (**275**) is much more stable (61TH1).

Fozard and Jones (65JOC1523) have discussed the then hypothetical, maximally unsaturated ring system of pyrido[1,2-a]azepine (**1**). Because a fully aromatic form of the parent substance must be excluded they expected some stabilization by a hydroxy group attached to the 10-position, in this

MS fragmentation of homoberbines
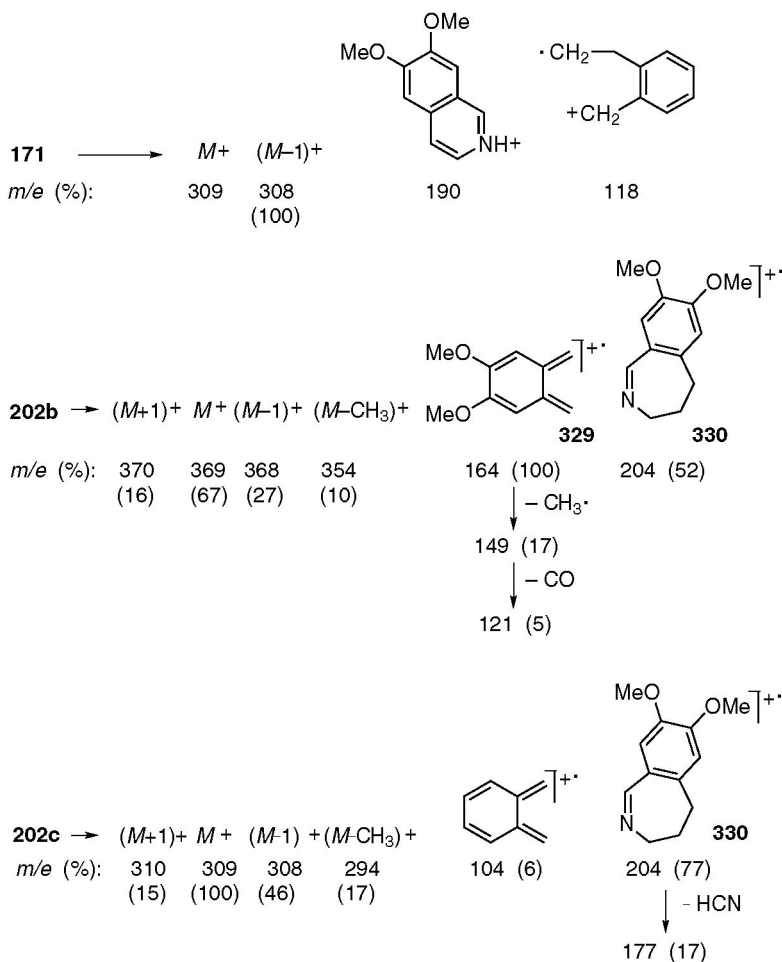
Scheme 74

way enabling mesomeric betaine forms. Proposed structures **309** and **310** of their products later had to be reformulated (see Section 2.8.1).

Azepino[1,2-*a*]isoquinoline **315**, finally obtained by Ebersbach's group (91HCA1095), has been described to be an unstable dark red oil that resists chromatography or crystallization but instead decomposes even at −20°C during a few hours. A small solvent influence in the electronic spectrum (Table 11) supports the assumption that dipolar structures do not significantly contribute to the ground level of potentially antiaromatic **315**.

3.4 Conformation

1-Azabicyclo[5.4.0]undecane (**2**) derivatives are usually conformationally described as consisting of a six-membered chair and a seven-membered deformed chair as in carbinols **331a** and **b** (Scheme 75) (76JPS1389). On the basis of IR and NMR spectra, *trans*-fused rings are proposed for both epimers, with the hydroxyl group of epimer **331a** in a quasiaxial position and that of **331b** in a quasiequatorial position. Other examples are those of conformations **15*** and **24*** of ketone **15** and carbinol **24**, respectively (71JHC7), and of a supposedly twisted conformation in the seven-membered ring of ketone **23b** (72OMR259).

NOE and NOESY experiments have established the stereochemistry of lactams **34a** and **b** (01TL6995) and of thioethers **368a** and **b** (see Scheme 84) (07T8267), respectively. The X-ray structure analysis of allene **77a** shows a half-chair conformation of the six-membered ring (92T2081).

Highly unsaturated base **292a**, on the basis of its NMR spectra and calculations, takes up structure **292a*** (97T14687). Broadened NMR peaks of lactams **288** and **290** indicate slow equilibria of two preferred conformations (91HCA1095).

In the field of conformationally restricted ACE inhibitors computer modeling predicts a minimum energy conformation for tripeptide analog **83** in which the fused phenyl ring is oriented in close proximity to the terminal carboxyl group (87MI1). Starting from ester **399**, stereoisomeric benzoylthiomethyl inhibitor precursors **403a** and **404a** (see Scheme 89) have been obtained, their relationship being different under basic (aprotic) and protic conditions (90TL815).
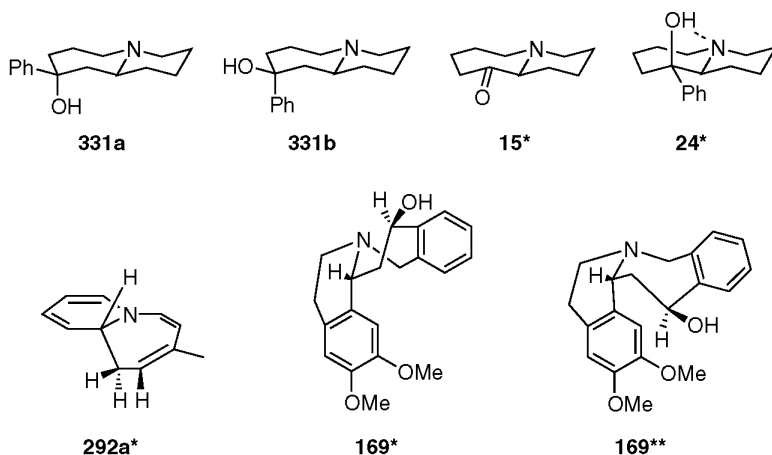
Scheme 75

Many homoberbines can take up three conformations: *cis-A* and *cis-B*, which turn into each other by a ring inversion, and *trans*, formed by a nitrogen inversion (e.g., 95LA567). Thus, X-ray analysis of homoberbine **202c** reveals the *cis-A* conformation. NMR data taken in solution at room temperature, however, favor an equilibrium of all three forms, whereas at 100°C, according to the results of the dehydrogenation by mercuric acetate (see Section 4.2.4) the *trans* form predominates. On the other hand, **205a** and **b** exist as *trans* forms in the solid state and again as a mixture of all conformers in solution at room temperature, whereas **205b** hydrochloride adopts a *cis-B*-fused conformation (97H(45)2137).

The *trans* or *cis* ring junction of rings B/C is indicated by the presence or absence, respectively, of IR Bohlmann bands (see Section 3.2.5). Additional results relate to homoberbines **173** (94LA1135), **177a** and **b** (97LA447), **179** (99PHA658), and **209b** (89LA1). According to calculations the *cis* conformation of homoscoulerine (**163**) is favored (98H(49)101). The Optical Rotation Dispersion and Circular Dichroism curves of homoberbines **426a** and **b** (see Scheme 93) were measured (69HCA1228). *cis* Ester **354a** is isomerized by base to *trans* ester **354b** (see Scheme 81) (03WO84963).

On the basis of NMR and IR spectra and the kinetics of the quaternization (see Section 4.2.5), homoberbine stereoisomers **169** are assigned the twist-boat conformation **169*** and the pseudo-chair conformation **169****, respectively (71T1363).

4. REACTIVITY

4.1 Salts and complexes

4.1.1 Ammonium and iminium salts

Many nonenamine bases give crystalline, well-defined hydrochlorides or hydroperchlorates, for instance, benzo derivatives **91** (65T2961) and **355** (see Scheme 81) (59JA2547) and homoberbines **157a** and **b** and **158** (69HCA1228), **173** (94LA1135), **177a** and **b** (97LA447), **202c** (95LA567), **205b** (97H(45)2137), **209a** and **b** (87LA639), and **367c** (see Scheme 84) (92JHC11). Astrocasine derivatives **9b** and **9c** form a dihydrochloride and dihydroperchlorates (65TL1761).

Enamines **274** and **260**, however, when protonated are transformed into pyridinium salt **273b** and iminium salt **261**, respectively (61TH1, 95LA567). IR shifts are typical of such transformations (see Section 3.2.5).

4.1.2 Complexes

When the synthesis of homoberbine **250** from amide **249** (see Section 2.6.1.2) proceeds with tin tetrachloride as Lewis acid at 60°C, a complex

250·SnCl$_2$ containing Sn(IV) is precipitated (00T993). The coordination of the metal to the carbonyls of the α-oxoamide functionality is suggested. Treatment with sodium hydroxide solution recovers base **250**. In the presence of titanium tetrachloride a similar complex **250**·TiCl$_2$ can be isolated. Carbinol **14a** gives a crystalline Reineckate, that is a salt of anion [Cr(SCN)$_4$(NH$_3$)$_2$]$^-$ (59AP143).

Crystalline charge–transfer complexes of aromatic polynitro compounds can likewise be used for isolating, purifying, and characterizing basic compounds. Thus, the 1,3,5-trinitrobenzene adduct of pyridone-methide **274** (61TH1), picrates of parent substance **2** (59CCC1846), ketone **15** (59AP143), and carbinol **24** (71JHC7), and the dipicrate of dihydrodesoxyastrocasine (**9c**; 65TL1761) were described.

4.2 Electrophilic reactions at pyridoazepine ring atoms

4.2.1 Substitution at saturated carbon atoms
Bromination of ketone **303** gives monobromide **304a** and dibromide **304b** (65JOC1523) whereas the electrochemical fluorination of parent compound **2** (84JAK59204192) provides a second, smooth path to perfluoro derivative **54** already mentioned.

According to patent descriptions (Scheme 76), activated methylene groups were reacted with nitrosating agents and with dimethylformamide to yield oximes, such as **332**, and α-aminomethylene ketone **334**, respectively (73USP3780043, 99WO32453).

4.2.2 Substitution at unsaturated carbon atoms
The electrophilic substitution of pyridones **187**, **192a**, and **193** (Scheme 77) yields bromide **335** (91MI1, 92MI1), bis-compounds, such as **336a** and **b** (87IJB1094), nitro derivatives **337** and **339**, and allyl compounds **340a** and **b**
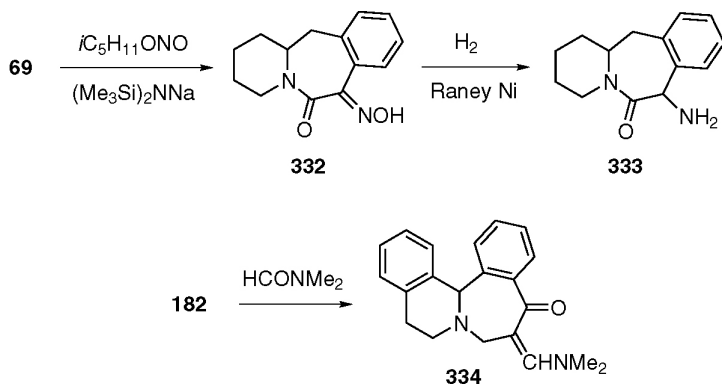
Scheme 76
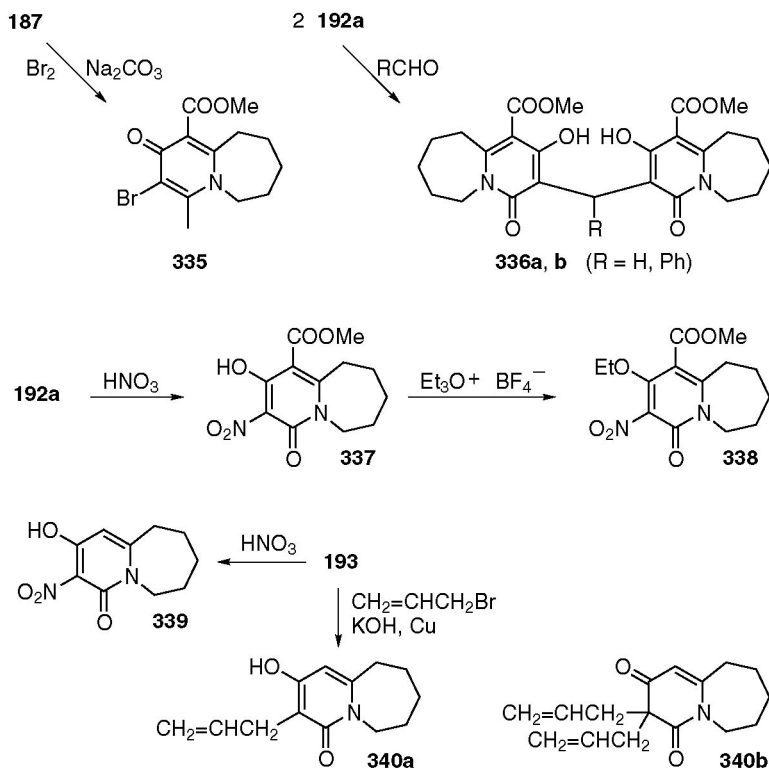
Scheme 77

(76IJB400). Dimers **336** form presumably via methylene or benzal intermediates, respectively, that undergo Michael addition.

Substitution of enamine **254** at the β-position gives acyl derivative **341** (Scheme 78) (03WO84963). Pyridoazepinone **288**, in the presence of different strong bases, could through deep red or green intermediates (**343a** and **b**, respectively) be deuterium labeled in the 4- and 7-position, respectively, to achieve deutero compounds **344a** and **b** (93H(35)817). 4-Benzoyl derivative **345** was also obtained. Deutero product **346** of maximally unsaturated base **315** forms smoothly in deuterium oxide (91HCA1095).

Pyridoazepinium salt **307** is brominated in the 7-position (65JOC1523).

4.2.3 Addition
Unstable enamine **274** could be stabilized by the formation of carboxanilide **275** (61TH1). Such a reactivity against isocyanates is known from pyridonemethides and other enamines (see, e.g., 24CB522, 78T2537). The formation of tetrabromide **347** serves to determine the structure of lactam **216a** (04CEJ3286).
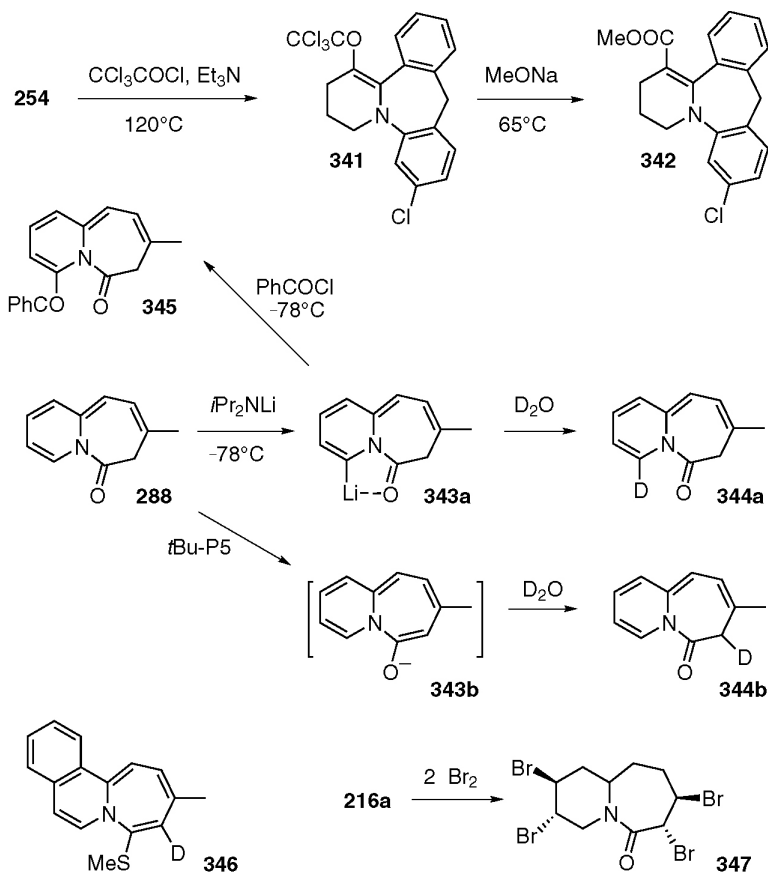
Scheme 78

4.2.4 Oxidation and dehydrogenation

Dehydrogenation with mercuric acetate introduces one or two double bonds into hexahydropyridoazepine-type homoberbines; treatment with perchloric acid yields fused dihydropyridinium or pyridinium salts, respectively (Scheme 79). In this way both species (**348a** and **b**) were obtained from homoberbine **173** as an inseparable mixture (94LA1135). Among isomeric dimethoxyhomoberbines, **177b** and **209b** in an analogous dehydrogenation yield iminium salt **349** and pyridinium salt **350**, respectively (97LA447, 89LA1, respectively) whereas **202c** affords iminium salt **351** together with by-product **263** that also spontaneously originates from enamine **260** and perchloric acid at 80°C (95LA567). Oxidation of the same **260** with potassium permanganate leads to isoquinolone **262**.
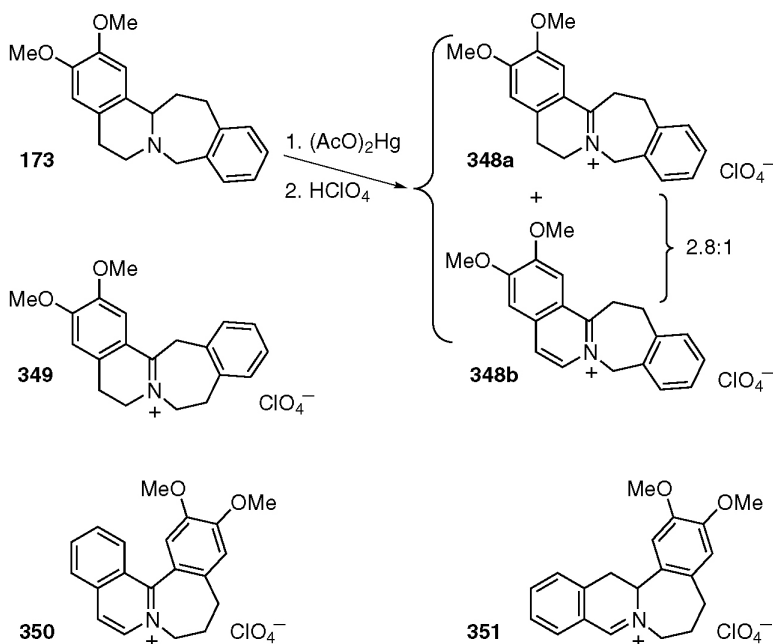
Scheme 79

An example of the 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) dehydrogenation is that of converting tricyclic **236a** to conjugated substance **236b** (87TL4929).

4.2.5 Quaternization

Well-crystallized methiodides serve to characterize nitrogen compounds, for example, in the case of hydrogenated parent **2** and its derivatives **14a** and **b**, which give salts **352a–c** (Scheme 80) (59AP143). Dihydrodesoxyastrocasine (**9c**) forms bis-quaternary salt **353c** (65TL1761).
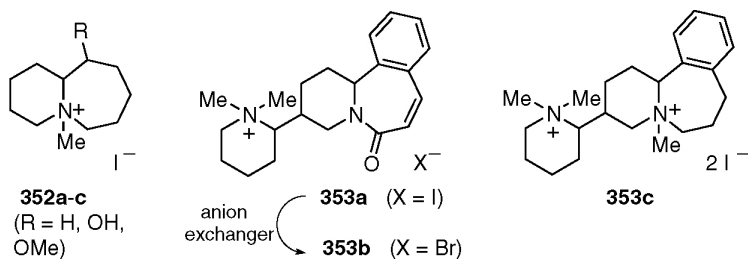
Scheme 80

High pseudo-first-order rates of methiodide formation were useful to verify the *cis*-B/C ring fusion in homoberbines, as in isomers **169** (2.3 and $3.1 \times 10^{-2}\,\mathrm{s}^{-1}$, respectively), **171** (3.4×10^{-2}), and **175** (1.5×10^{-2}), while the rate is close to $5 \times 10^{-3}\,\mathrm{s}^{-1}$ for a *trans*-fused analog (71T1363). Homoberbines **155** and **202b** and **c**, for instance, give methiodides **422** and **411b** and **c**, respectively (see Schemes 92 and 91) (77CPB2510, 10AP207), **181** and **209a** yield **413a** and **415a** (07JME4528), and **209b** affords **415b** (03H(60)887).

4.3 Reduction and hydrogenation of the pyridoazepine rings

The hydrogenation of partially unsaturated amines **25**, **89a** and **b**, **95b**, and **374a** and **b** (see Scheme 85) on palladium or iridium catalysts leads to base **26** (71JHC7), to a stereoisomerically *cis*-enriched mixture of lactams **90a** and **b** (02S87), to trihydroxy **95c** (10OBC2639), and to lactams **376** and **377** (08TL5141), respectively. Reduction and hydrogenation products of natural astrocasine (**8**) are depicted in Scheme 4 (Section 2.2; 65TL1761). Accompanying substance astrocasidine (**9d**) is in two steps hydrogenated finally giving stereoisomeric tetrahydro products, one of which is identical with dihydroastrocasine (**9a**) (72AQ769).

An example of enamine reduction is that of tetracyclic ester **342**, which leads to *cis* compound **354a** and, on subsequent epimerization, *trans* derivative **354b** (Scheme 81) (03WO84963). The enamine double bond is also reduced in the case of **246** (to give **247**) and **248** (05CC3071) and **269a** and **b** and **270b** (to give **271a** and **b**) (84BF(2)317). Contrarily, the heterogeneous
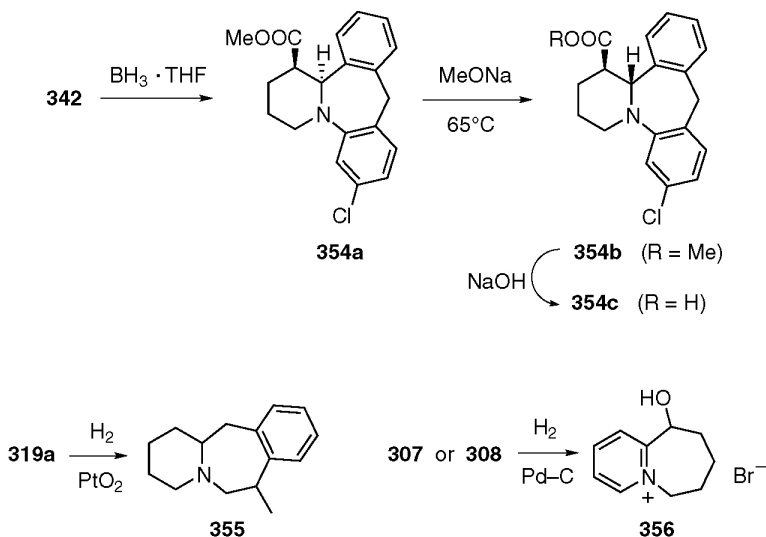
Scheme 81

catalytic hydrogenation of dihydropyridone **124a** attacks only the non-enamine double bond to yield enamine **125** (01J(P1)1435).

The stereocontrolled reduction or hydrogenation of enamine **107** leads either to *cis*-**108** (with NaBH$_4$ at 25°C or H$_2$/Raney Ni at 100°C) or to *trans*-**108** (with H$_2$/Raney Ni at 200°C) (90H(31)1251). Ketoenamine **256** is reduced to hydroxyamine **257** (07WO25938).

Iminium salt **60** when reduced yields 1-azabicycloalkane **2** (03T3099), while hydrogenation of morphanthridizinium salt **319a** leads to a mixture of diastereomers **355** (59JA2547). The partial hydrogenation of bromoazepine **307** and **308** is accompanied by debromination to give pyridinium salt **356** (65JOC1523). An analogous deiodination was observed during the hydrogenation of mixture **29a**/**29b** affording lactam **30a** (94TL393).

4.4 Introduction and transformation of individual substituents at the pyridoazepine rings

4.4.1 Carboxylic and derivative groups

In the bicyclic pyridoazepine series hydrolysis and partial decarboxylation of diester **39a** followed by reesterification gives isomeric monoesters **39b** (79JOC4173).

In the series of ACE inhibitors (see Scheme 21) ester **81a** is obtained by the reaction of carboxylic acid **84a** with diphenyldiazomethane (87MI1) or benzhydrylbromide and cesium carbonate (95WO14663). Benzylbromide/Cs$_2$CO$_3$ leads similarly to the benzyl ester (97WO38705). Selective cleavage of benzhydrylester **82a** with trifluoroacetic acid gives prodrug **82b**; further hydrolysis with lithium hydroxide yields diacid **83** (87MI1). The latter reagent also transforms ester **402a** (see Scheme 89) to acid **402b** (90TL815). The introduction of a carboxyl group into enamine **133** is accomplished by means of a carbonylation–hydration sequence with formic acid or carbon monoxide under pressure to afford epimers **357** (Scheme 82) (96WO19492).

The methanolysis of trichloroacetyl dibenzopyridoazepine **341** leads to methyl ester **342** (03WO84963), whereas hydrolysis and esterification of nitrile isomers **369** (see Scheme 84) gives ethyl esters **370** (96BMC255). The reduction of the ester groups in *cis–trans* isomer couples **108** and **370** affords *β*-aminoalcohols **358** (90H(31)1251) and **371** (96BMC255), respectively. Hydrolysis of pyridone ester **192a** gives free acid **192b**, which can easily be decarboxylated to yield pyridone **193** (76IJB400).

Carboxanilides, such as **359**, are obtained from **335**-type precursors (91MI1, 92MI1). Amidation of protected chiral educt **360** proceeds via coupling to protected aspartyl aldehyde synthon **361** followed by successive removal of the *tert*-butyl ester and semicarbazone protecting groups to yield inhibitor **362** (98BML2757).
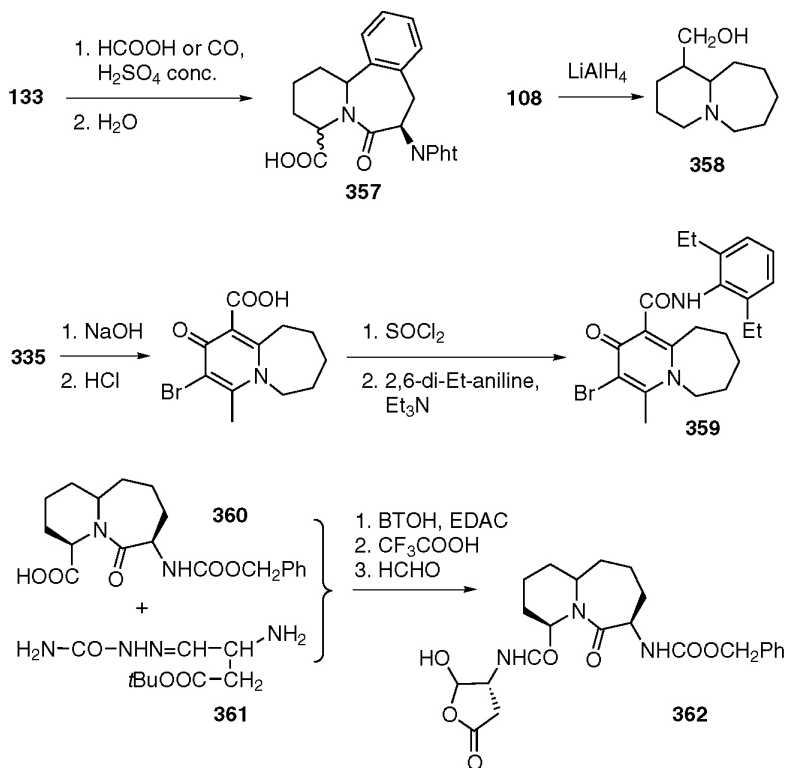
Scheme 82

4.4.2 Carbonyl groups

Aldehyde **10a** [derived from astrocasine (**8**) by degradation] is oxidized with silver oxide to acid **10b**, and it can be characterized as a 2,4-dinitro-phenylhydrazone (65TL1761). Among similar derivatives are oximes of ketones **15** (59AP143) and **303** (oxime **363**, Scheme 83) (65JOC1523), oxime and *O*-(aminocarbonyl)oximes of homoberbine **182** (73USP3780043), and mono-(2,4-dinitrophenylhydrazones) of ketolactams **22** (62CPB366) and **31** (80T143). Quinolonemethide **232** generates phenylhydrazone **365** and hydrazone cyclization product **366** (83UKZ185).

Hydrogenation of ketone **303** gives carbinol **364** (65JOC1523) whereas sodium borohydride reduces saulatine (**11**) to the respective hydroxylac-tam (84JNP539). Ketonic homoberbine **174** is also hydrogenated to carbinol **175** while hydrogenation (H_2/PtO_2) or reduction ($NaBH_4$) of ketolactam **168** give rise to mixtures of epimers **167** in the ratio of 2:3 and 1:10, respectively (71T1363).

The transformation of the carbonyl group to methylene in ketoamine **15** (to yield **2**) proceeds by means of the Wolff–Kishner reaction (59AP143).
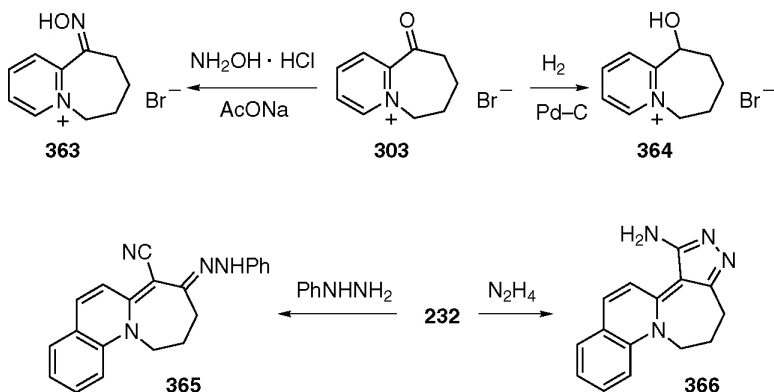
Scheme 83

The exhaustive reduction of lactams was preferentially managed by lithium alanate, for instance, with **20** to get **2** (59CCC2318), with **8** and **9a** to get **9b** and **9c**, respectively (65TL1761), with single epimers **167** to get epimers **169**, and with **170** to get **171** (71T1363).

Modern reduction reagents include diborane used, for instance, to generate dibenzo-fused **177b** and **c** (Scheme 84) (92JHC11) or **272a** and **b** (84BF(2)317) from lactams **178b** and **c** and **271a** and **b**, respectively, and borane dimethylsulfide complex that reduces, for example, lactam **134** to parent substance **135** (01H(55)1519). Sodium triacetoxyborohydride reduces ketolactam **375** (see Scheme 85) stereospecifically to hydroxylactam **373b** (08TL5141). Simple bicyclic ketone **23a**, after reacting with ethanedithiole, with Raney nickel forms parent substance **2** (10CC3351).

Grignard reactions of ketones **15** and **23a** give rise to carbinol **24** (71JHC7) and the mixture of epimeric carbinols **331a** and **b** (76JPS1389), respectively. Lactam **144b** is by the reaction with methyl lithium and reduction converted to *cis* and *trans* **358a** and **b** (07T8267). Treatment of ketone **3** (and analogously **23a**) with tosylmethyl isocyanide gives an inseparable mixture of isomers **369** (96BMC255).

4.4.3 Hydroxyl and derivative groups

The reactions of potential alkaloid precursor **150a** as depicted in Scheme 85 (upper part) include several relevant transformations (08TL5141): acetylation (from **373b** to **150b**), deacetylation (from **150a** to **373a**), mesylation (from **373a** and **b** to **374a** and **b**), benzylether cleavage (from **374a** by hydrogenation to **376**), and oxidation [from **373a** by Dess–Martin periodinane (DMP) to **375**].

Other ester forming reactions lead to acetate **229b** (61TH1), to the propionates of carbinols **24** and **331a** (71JHC7, 76JPS1389), and to the
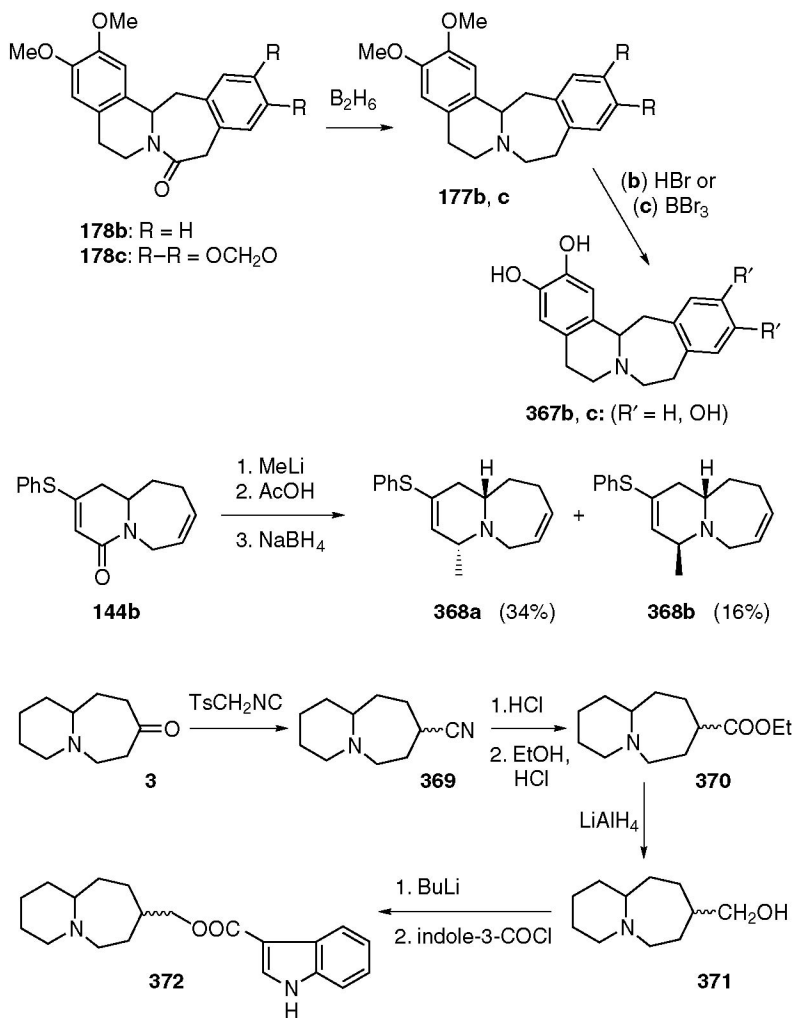
Scheme 84

3,5-dinitrobenzoate of carbinol **14a** (59AP143). The *O*-acetylation of pyridinium salts **303** or **304a/b** is accompanied by enolization and dehydration, respectively (65JOC1523). Geminate dihydroxy compounds **304a** and **b** form hemiketals **381a** and **b** (Scheme 86).

Ether **14b** when cleaved affords carbinol **14a** (59AP143). Enamine ether **145** presents an alkoxy group adjacent to nitrogen, which suggests the generation of dihydropyridinium intermediate **382**, a quasi vinylogous acyliminium cation; indeed allyl- and allenylenamines **383a** and **b** were obtained (09CEJ4565).
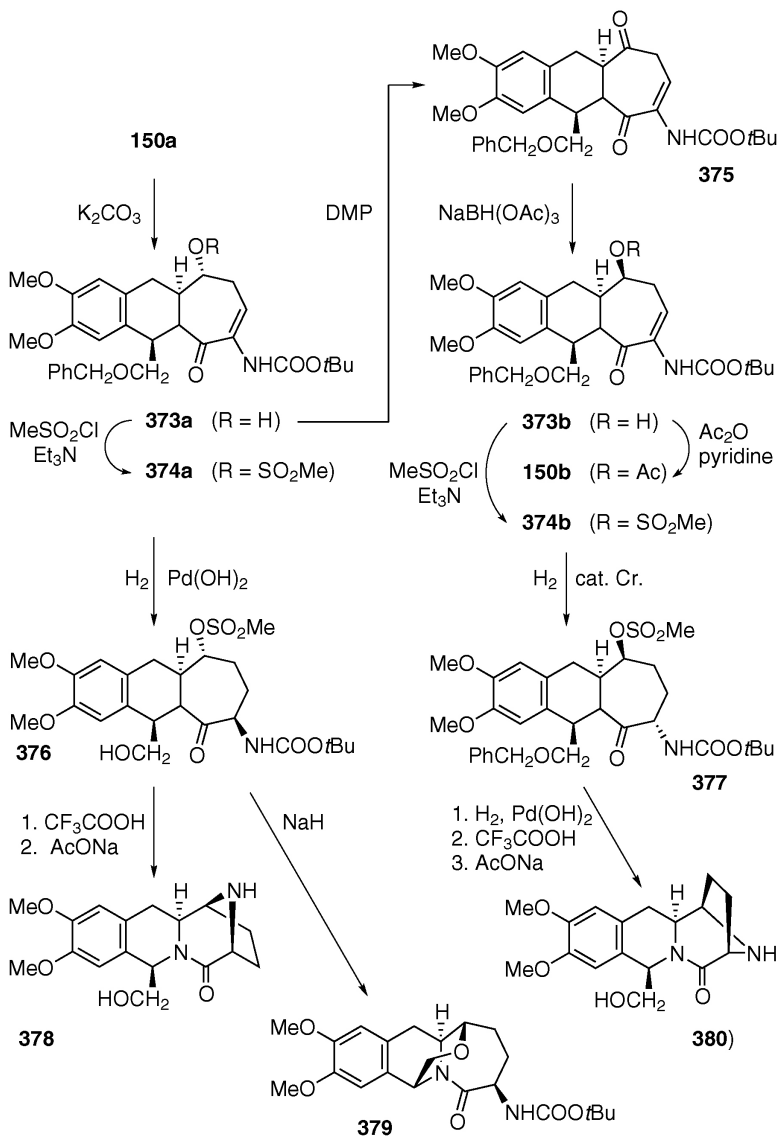
Scheme 85

Hydroxypyridone **337** by triethyloxonium fluoborate was transformed to ether **338** that resisted nucleophilic reactions (76IJB400). Such reactions were possible, however, in the case of pyridone **192a** through chloro compound **384**. Nucleophilic displacement of triflate **28** resulted in the formation of iodide **29a** as the major product (94TL393).
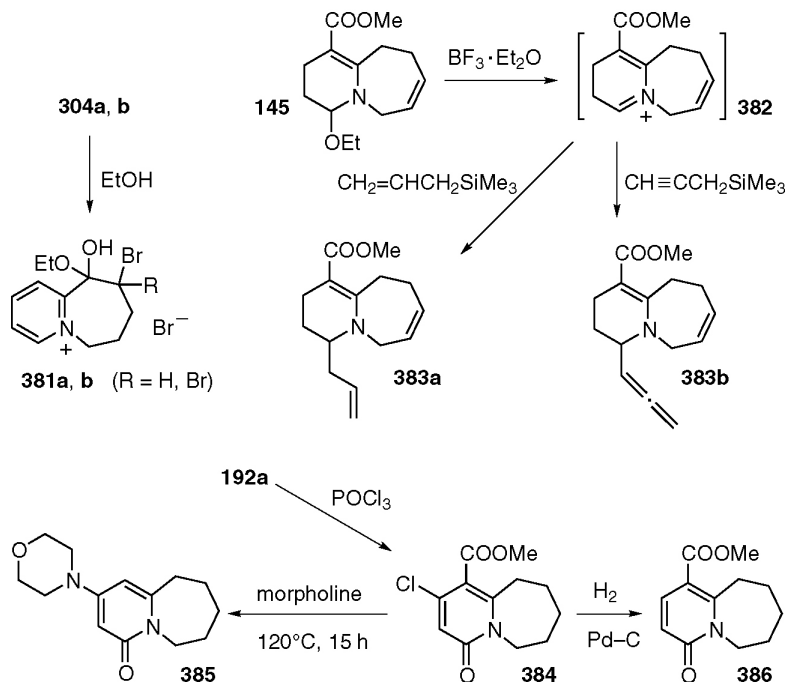
Scheme 86

Further reactions of hydroxy groups involve the oxidation of carbinol **14a** to ketone **15** (59AP143), oxidation and reduction of homoberbine epimers **167** to ketolactam **168** and lactam **170**, respectively (71T1363), and dehydration of carbinol **24** (71JHC7).

4.4.4 Sulfur-containing groups
The formation and reactions of thiolactam **313** have been depicted in Scheme 70 (cf. Section 2.8.1).

4.4.5 Nitrogen-containing groups
The synthesis of amines from oximes is exemplified by the reduction of oxime **332** to **333** (99WO32453) and of bicyclic oximes (derived from ketones **3** and **23a**), for instance, of oxime **387** (Scheme 87) to amine **388** that is acylated to yield potential pharmaceutical agent **390** (92BML1147). Nucleophilic substitution of chloropyridine **384** generates morpholino derivative **385** (76IJB400).

Two examples illustrate the formation of amino groups at 1- or 2-positions of dibenzopyridoazepines: the route from carboxylic acid **354c** by Curtius degradation through mixed anhydride to yield amine **391**
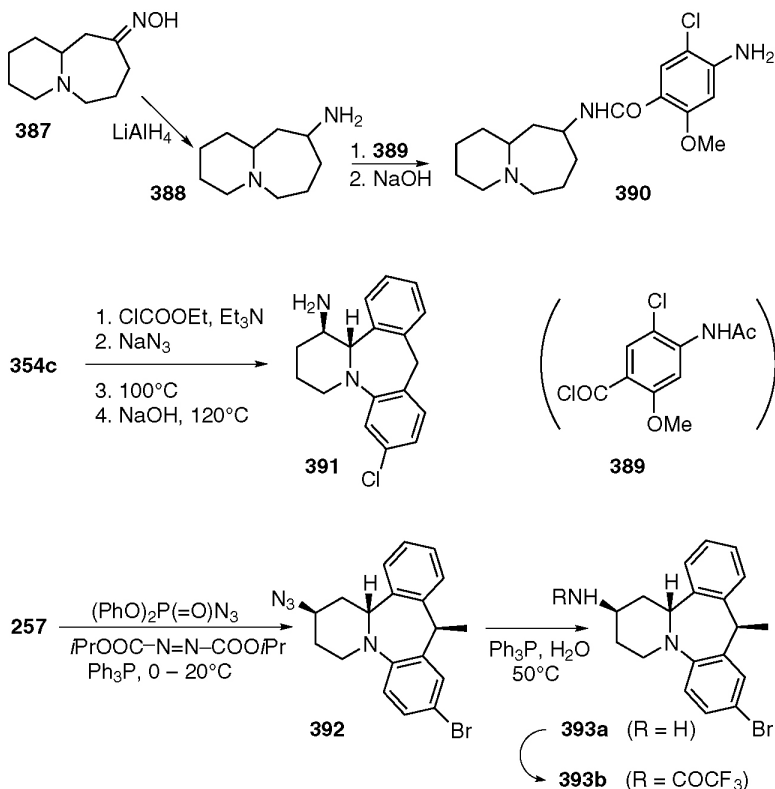
Scheme 87

(03WO84963) and the reaction of carbinol **257** with diphenylphosphoryl azide in the presence of azodicarboxylate and triphenylphosphine through azide **392** to afford amine **393a** and subsequently amide **393b** (07WO25938). Amine **391** with ethyl trifluoroacetate/triethylamine or trifluoroacetanhydride/pyridine gives the trifluoroacetamide, too (cf. 08BML1461).

The groups of Flynn and Robl described the syntheses of potential ACE inhibitors by amidation of **30a**-type and **81a**-type α-aminolactam esters (after N-deprotection by hydrazine) and other reactions (Schemes 88 and 89). In this way mercaptoacyl-containing substance **394b** was made by BT-OP⁺(NMe₂)₃ PF₆⁻ (BOP)-mediated coupling of amine dipeptide surrogate **30b** with α-acetylthiohydrocinnamic acid and saponification of the acetate and ester groups in intermediate **394a** under strictly oxygen-free conditions (96JME494).

In the tricyclic inhibitor series amidation of benzhydryl ester **81b** with phenyllactic acid or mono-*tert*-butyl β-benzylsuccinate gives **395** (92EPP481522) and **396** (95USP5455242), respectively. A similar amidation
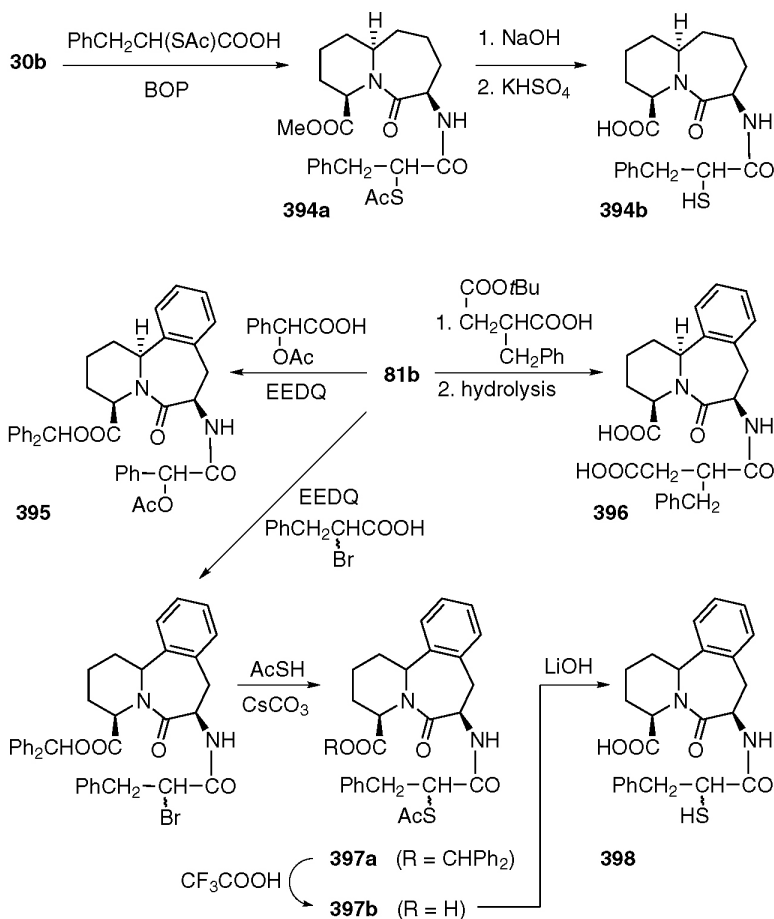
Scheme 88

with (R)- and (S)-α-bromohydrocinnamic acids, respectively, and subsequent twofold ester hydrolysis lead to epimeric target thiol inhibitors **398** (93JME2420). Analogous methyl ester **399** after coupling with a hydroxyl-amine-containing hydrocinnamic acid derivative finally yields N-formyl **400b** (00BML257).

On the other hand, α-aminolactam ester **399** is converted, by the decomposition of α-diazolactam intermediate **401**, to unsaturated lactams **402a** and **b** that finally yield epimeric mercaptomethyl inhibitors **403b** and **404b** (90TL815).

Beside amidation, N-alkylation serves to couple aminolactam **81b** to a side chain, as by S$_N$2 displacement of 2-hydroxy-4-phenylbutyric ester triflate, to yield amino acid ester **82a** (87MI1).
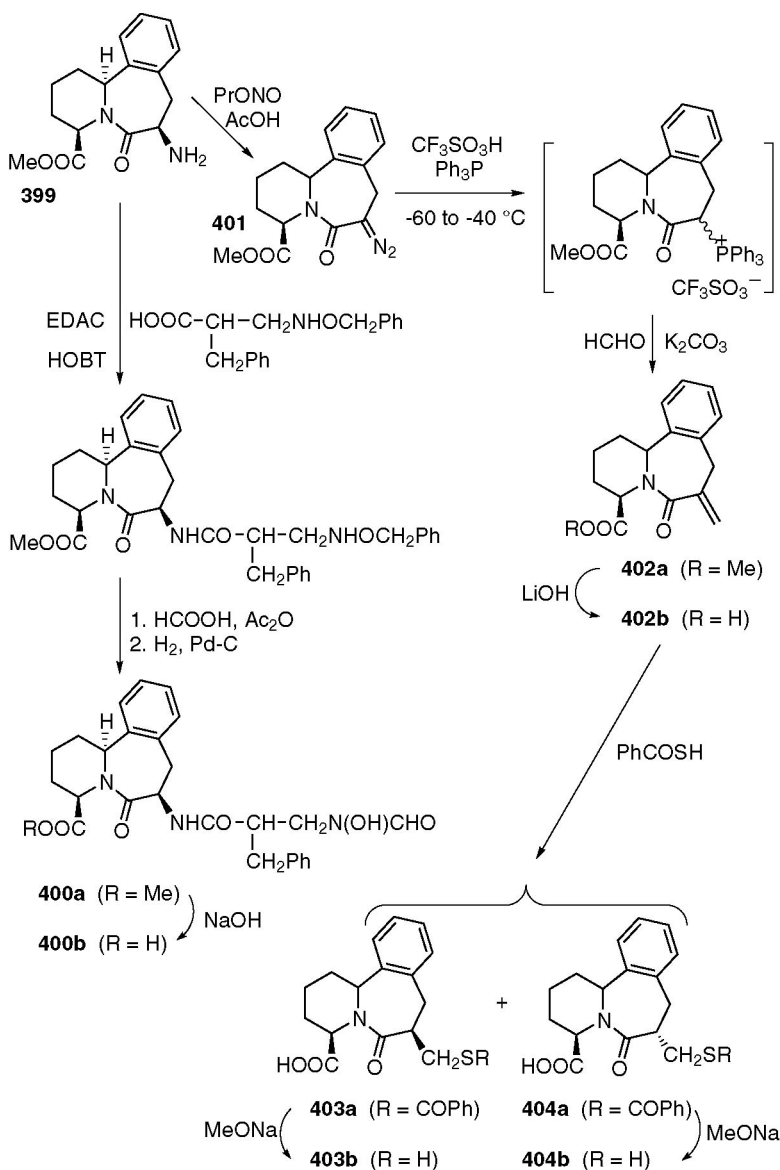
Scheme 89

4.4.6 Elimination

Reductive elimination of halogen or pseudohalogen occurs with iodide **29a** (94TL393), cyanide **228a** (01CCL7), chloride **384** (76IJB400), and the bromide derived from carbinol **17** (59CCC1846). The trimethylsilyl group

of homoberbine **226a** is eliminated by means of ammonium fluoride (99JOC4830).

4.5 Cleavage, transformation, and formation of rings

4.5.1 Cleavage of the seven-membered ring

Pyridoazepinium salts **307** and **308** are cleaved by base to yield pyridoyl-butadienes **312** and **311**, respectively (82JOC2792). The relevant reactions of pyridoazepinone **288** and its benzolog **290** (Scheme 90) involve the cleavage of the lactam bonds and subsequent rearomatization to form pyridines and isoquinolines, respectively (91HCA1095, 93H(35)817).
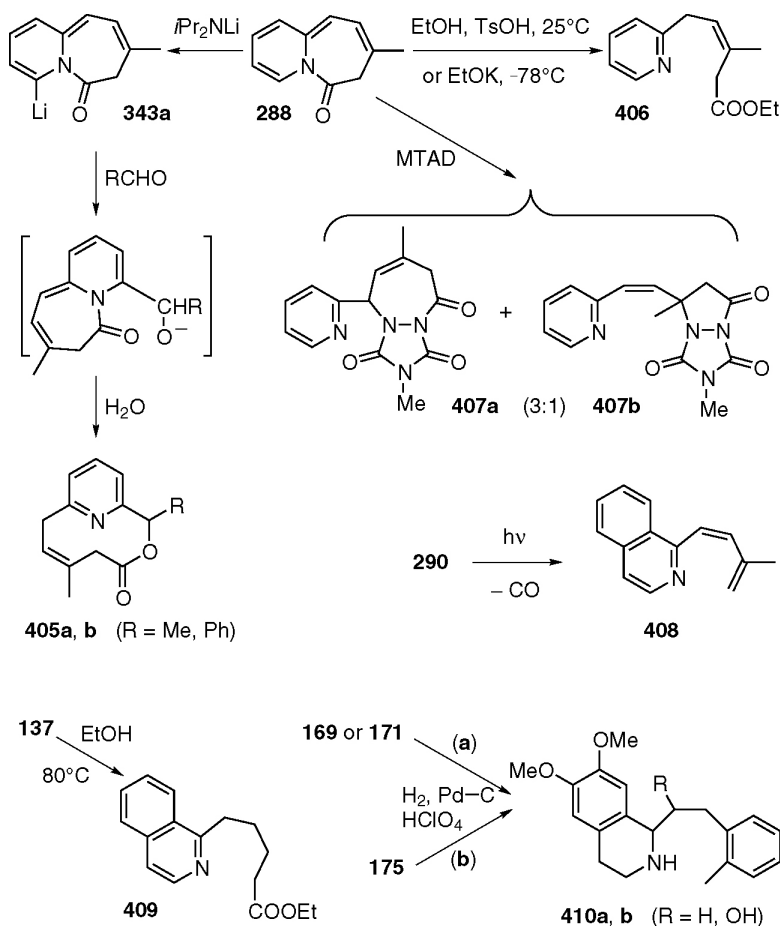
Scheme 90

Hence, lithium salt **343a** is trapped by aldehydes, and subsequent intramolecular attack of the intermediate alkoxide on the lactam moiety leads to pyridinophanes **405a** and **b**. Ethanolysis of lactam **288** under acidic or basic conditions, even at $-78°C$, affords ester **406**, whereas the reactions of lactams **288** and **290** with 4-methyl-1,2,4-triazoledione (MTAD) give mixtures of cycloadducts **407a** and **b** or the respective isoquinolines. Tricyclic **290** when irradiated suffers loss of carbon monoxide to form butadiene **408**.

Solvolysis of lactam **137** accompanied by elimination of cyanide gives ester **409** (72JHC541). Hydrogenolysis of homoberbines **169/171** or **175** yields phenethylisoquinolines **410a** and **b**, respectively (71T1363). Analog **157b**, however, does not undergo this reaction, presumably for steric reasons because of the substitution at C-9.

The exhaustive oxidative degradation of the pyridoazepine ring system serves to elucidate structures. Treatment of morphanthridizinium salt **319a** (59JA2547) or isomorphanthridizinium salt **322a** (61JOC3278) with alkaline potassium permanganate leaves phthalic anhydride and 4-methoxyphthalic acid, respectively. After oxidizing astrocasine (**8**), phthalic and phthalonic acids together with aliphatic C_2- to C_5-dicarboxylic acids were isolated (65TL1761).

4.5.2 Cleavage of the nitrogen–carbon bridge

The cleavage of the central nitrogen–carbon bridge in homoberbines to yield 1-azaundecadiene or -triene derivatives (Scheme 91) is commonly accomplished with quaternary salts. Thus, methiodide **411b** with dimsyl sodium gives triene **412**, presumably via hydrogen abstraction at C-14 position and Hofmann degradation (77CPB2510). More frequently, however, Birch conditions are chosen, for instance, to transform chloro derivatives **413a** and **b** to **414a** and **b** (under dechlorination) and compounds **415a** and **b** to **416a** and **b** (03H(60)887, 07JME4528) or to split quaternary salt **411c** (10AP207).

Treatment of precursor **209a** (nonmethylated at N) with chloridocarbonate and a reducing agent has proven to be a milder method for cleaving the nitrogen–carbon bond; this reaction was followed by splitting off urethane and ether groups with boron tribromide to yield target **417**. When tetrahydroxylated base **367c** (92JHC11) is subject to autoxidation it turns yellow, presumably because of transmutation into a highly conjugated compound, such as **418**.

4.5.3 Ring contraction

Ring-contracted substance **419** (Scheme 92) arises from quinoline **123b** under conditions that also favor, in the case of the tetrahydropyranyl-substituted analog **123a**, the formation of evasive product **419**
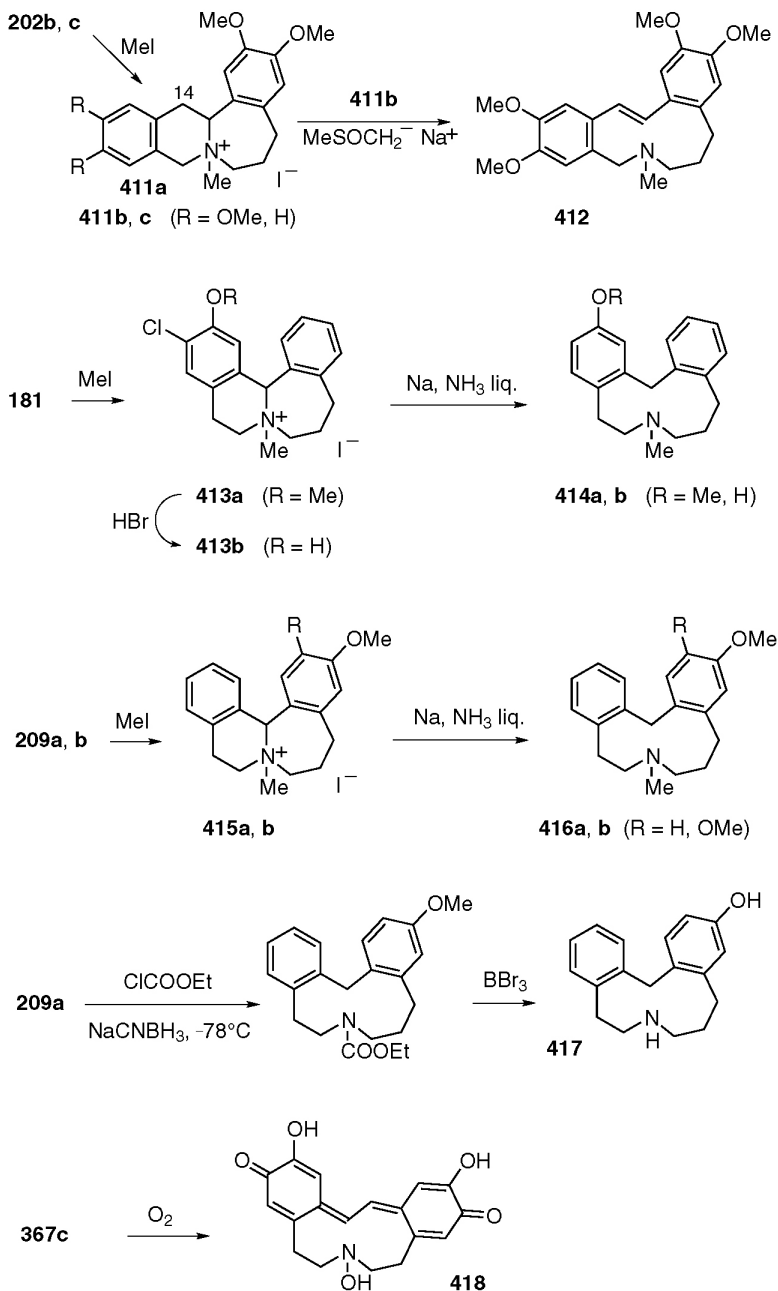
Scheme 91
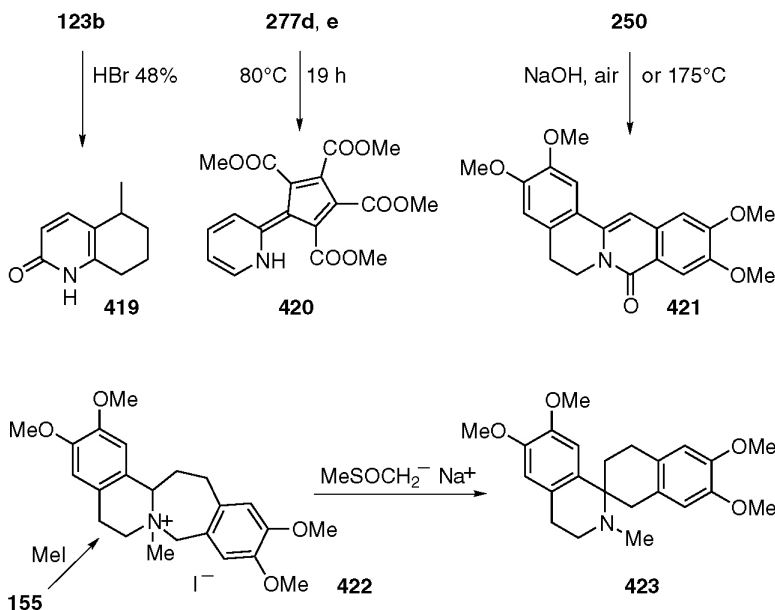
Scheme 92

(86JOC2184). Heating tetraesters **277d** or **e** gives fulvene **420**, presumably by 1,3-shifts and elimination of acetic or benzoic acid, respectively (79J(P1)584). Dibenzo derivative **286a** similarly forms quinophthalone dye **286b** (10JAK143896).

Homoberbine diketones, such as **250**, undergo decarbonylation by a benzylic acid-type rearrangement and oxidative decarboxylation to afford target 8-oxoprotoberberine **421** (8-oxopseudopalmatine) (00T993). Homoberbine methiodide **422** (different from analog **411b**), when treated with dimsyl sodium, affords expected spiroisoquinoline **423** (77CPB2510).

4.5.4 Ring bridging

Intramolecular S_N2 reactions of lactams **376** and **377** (see Scheme 85, lower part) produced nitrogen- and oxygen-bridged, highly strained products **378, 379,** and **380,** forming densely functionalized tetracyclic frameworks of the tetrahydroisoquinoline alkaloids (08TL5141).

4.6 Reactivity of side-chains and fused benzene rings

4.6.1 Side chains

Oxidizing splitting of olefinic side chains forms dione **22** from benzal **21** (62CPB366) and aldehyde **10a** from quaternized and Hofmann-degraded

lactam **9a** (65TL1761). Esterification of hydroxymethyl **371** gives agent **372** (96BMC255).

Amide **425** (an isomer-homolog of **390**) is obtained from amine **424** (Scheme 93) (81EPP36269). The piperidine substituent in astrocasine (**8**) and derivatives **9a**, **9c**, and **9d** is quaternized to yield, for instance, salts **353a** and **353c** (65TL1761, 72AQ769). Iodide **353a** in solution, on passing an anion exchange column pretreated with potassium bromide, is transformed to bromide **353b** (76JOC2454).

4.6.2 Fused benzene rings
In the homoberbine series, both acid-catalyzed partial cleavage of pentamethyl ether **157a** and acid debenzylation of monobenzyl ether **157b** yield monohydroxy **158** (69HCA1228). Further, the stereoisomers of dibenzyl ether **426a** when debenzylated give dihydroxy derivatives **426b** that on methylation again yield ether **157a**. The cleavage of ethers **177b** and **c** (to
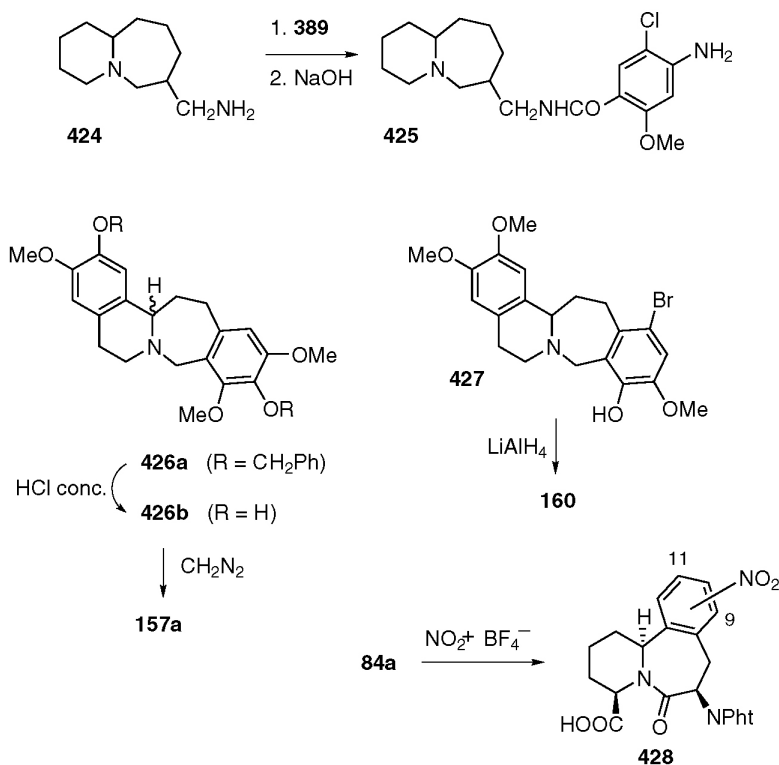
Scheme 93

give **367b** and **c**) (92JHC11) and that of quaternized **413a** (to give **413b**) and **415a** (07JME4528) was also reported.

Related homoberbine derivative **427**, when debrominated, provides a second access to target **160** (69JC874). Finally, inhibitor precursor **84a** on nitration gives 9- and 11-nitro derivatives **428** (27 and 64%, respectively); after esterification, deprotection, and amidation (analogously to the formation of **82a** from **81a**), reduction (H$_2$, Pd–C) affords the respective amino or sulfonylamino compounds (92EPP492369, 94WO28901, respectively).

5. APPLICATIONS

5.1 Pharmaceutical uses

A series of bi- and tricyclic pyridoazepine-type lactams was studied as conformationally restrained peptide mimetics acting as ACE inhibitors or dual inhibitors, that is both ACE and neutral endopeptidase (NEP) inhibitors, especially by the groups of Flynn and Robl. ACE and NEP are zinc metalloproteases acting as vasopeptidases. The respective inhibitors are used in the treatment of hypertension, congestive heart failure, and other cardiovascular diseases.

Among bicyclic compounds mercapto amide **394b** is one of the most potent substances (96JME494, 97JME1570). Amidolactam **362**, on the other hand, is an excellent selective, reversible inhibitor of enzymes caspase-1 and caspase-3 (98BML2757).

Particular emphasis has been placed on benzo-fused analogs, at first amino acid-type compound **83** or MDL 27088, formed from prodrug **82b** or MDL 27210 (87MI1, 92JPS1071); agent **83** was then the most potent ACE inhibitor (93AGE1244). Later the main interest has focused on mercaptoamide-type dual ACE and NEP inhibitor (*S*)-**398** or MDL 100173 and prodrug (*S*)-**397b** or MDL100240 that exhibit a balanced activity on both enzymes (93JME2420, 94MI1, 96JA8231, 99MI1, 03MI1). Methods based on HPLC with UV detection were developed to quantify both substances in plasma (95JCH(B670)91).

Examples of other ACE or dual inhibitors having mercapto or acylmercapto pharmacophores are those of epimers **403b** and **404b** (90TL815), thioesters **429a** (Scheme 94) or MDL101264 (95WO25532) and **429b** or AVE 7688 (08MI1), and sulfonamides derived from nitro compounds **428** (94WO28901). Together with carboxy and mercapto groups, *N*-formylhydroxylamine was found to be an excellent zinc-chelating entity, namely in the case of inhibitor **400b** (00BML257).

In a recent study on the scaffold-hopping potential of fragment-based *de novo* design, among ACE inhibitors known lead structures **397b** and
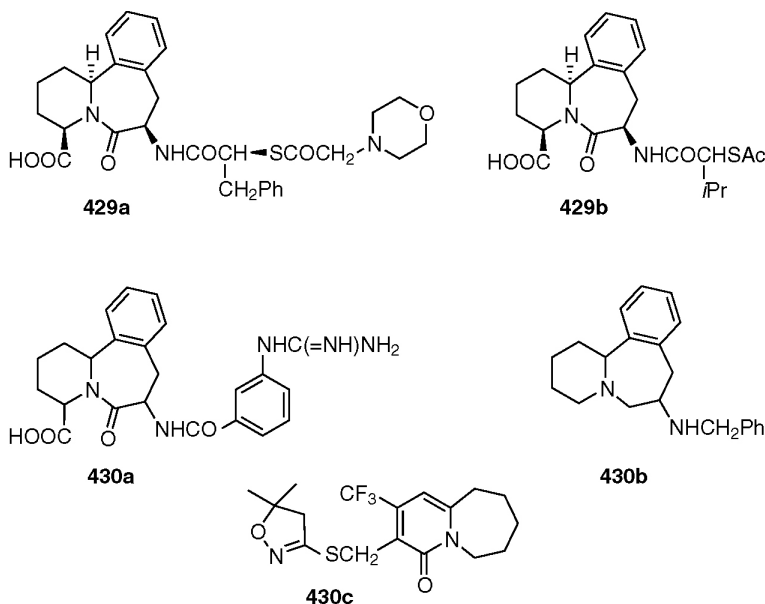
Scheme 94

429b were reconstructed; then novel chemotypes **430a** and **b** could be generated (09CCT383). Moreover, MDL 100173 (**398**) was included in a study of the binding mode of representative dual ACE/NEP inhibitors (10MI1).

Several homoberbines were reported to exhibit pharmacological activities: homoscoulerine (**163**) is a potent antimalarial agent the 9-positioned hydroxyl group playing a significant role in this activity (98H(49)101). Diketoenamine **250** shows distinct cytotoxicity (00T993). Homoberbines **181** and **209a** do not display affinity for dopamine receptors whereas nitrogen–carbon bridge splitting products **414a**, **416a**, and **417** and similar compounds are potent dopamine receptor antagonists (07JME4528, 10AP207). Hydroxylactames, such as **71**, are claimed to be transquilizers (74USP3824244).

5.2 Agrochemical uses

Among various 4-pyridone 3-carboxanilide derivatives, pyridoazepines, such as **359**, were found to possess high light-dependent herbicidal activity (91MI1). Quantitative structure–activity relationships regarding the substitution at the pyridone and anilide moieties of such compounds were examined (92MI1, 92MI2). Sulfide **430c** is an example of heterobicyclic isoxazolines claimed for weed control (10USP99561).

LIST OF ABBREVIATIONS (CF. SCHEMES 95 AND 96)

acac   acetylacetonate
ACE   angiotensin-converting enzyme
AIBN   azobisisobutyronitrile
BBEDA   bis(benzylidene)ethylenediamine
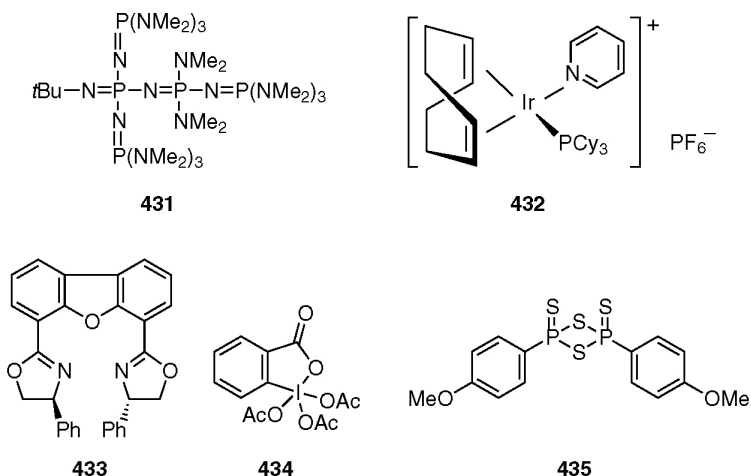
Scheme 95
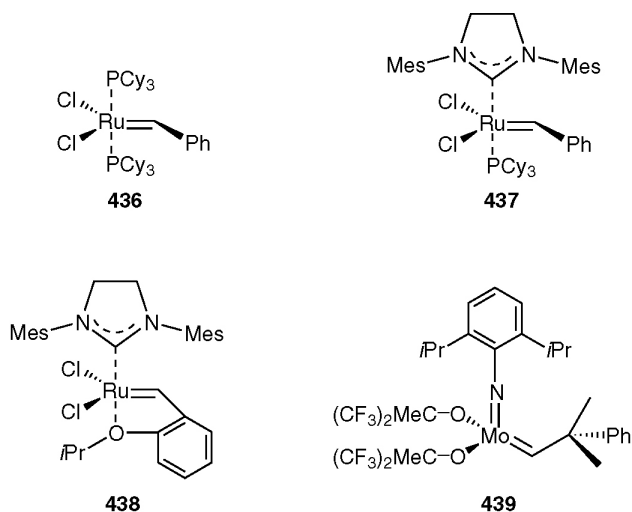
Scheme 96

BDN	1,8-bis(dimethylamino)naphthalene (proton sponge)
BOP	BT-OP$^+$(NMe$_2$)$_3$ PF$_6^-$
BT	benzotriazol-1-yl
*t*Bu-P5	phosphazene base **431**
cat. Cr.	Crabtree catalyst (**432**)
cat. Gr. I	first-generation Grubbs catalyst (**436**)
cat. Gr. II	second-generation Grubbs catalyst (**437**)
cat. Gr. H.	Grubbs–Hoveyda catalyst (**438**)
cat. Sch.	Schrock catalyst (**439**)
cod	1,5-cyclooctadiene (ligand)
cp	cyclopentadiene (ligand)
CPBA	*m*-chloroperbenzoic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBFox	di(oxazolinyl)dibenzofuran ligand **433**
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMP	Dess–Martin periodinane (**434**)
EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EEDQ	1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
HOBT	1-hydroxybenzotriazole
LR	Lawesson reagent (**435**)
Mes	mesityl
MTAD	4-methyl-1,2,4-triazoledione
NEP	neutral endopeptidase
NOE	Nuclear Overhauser Effect
PhtN	phthalimido
PPA	polyphosphoric acid
RCM	ring-closing metathesis
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
Tol	*p*-tolyl
Ts	*p*-toluenesulfonyl

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CHAPTER **3**

Synthesis, Structure, Chemical Reactivity, and Practical Significance of 2-Amino-4*H*-pyrans

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1. INTRODUCTION

The class of 2-amino-4*H*-pyrans has been known for several decades. The first representatives **1** and **2** are from the late 1950s to the early 1960s. Spiro-conjugated pyranopyrazole **1** was obtained in studies on pyrazolone dyestuffs (56ACS587), while pyranopyranone **2** served as a precursor for the blood anticoagulant warfarin (62JOC3086).
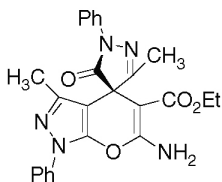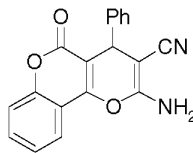
1   1956   **2**   1962

The formation of the pyran ring, bearing an amino group in position 2, tends to be reversible. The presence of a strong electron-withdrawing substituent in position 3 (e.g., CN, COR, CO$_2$R) seems to be crucial for the stability of these compounds. There are no reliable data on 3-unsubstituted or 3-alkylsubstituted 2-amino-4*H*-pyrans. Since the middle 1970s there has been rapid progress in the chemistry of 2-amino-4*H*-pyrans, studies on their physicochemical properties, as well as various types of biological activity. In recent years, modern techniques were applied to aminopyran synthesis: catalytic electrogeneration, microwave and ultrasonic assistance, the use of "green" solvents, and solid-phase synthesis. Reviving interest in 2-aminopyrans can be attributed to the discovery of new types of biological activity, including recent pronounced anticancer. Progress in the chemistry of 2-amino-4*H*-pyrans is partly reflected in reviews (78S241, 83AHC145, 98RCR393, 02WO092594, 08S1, 09AHC1), monographs (85MI1, 03MI1), and Ph.D. theses (02MI1, 03MI2, 04MI1). Till now, there were no attempts to completely review 2-amino-4*H*-pyrans. In this review, we provide a comprehensive literature survey on the chemistry and applications of 2-amino-4*H*-pyrans from 1950 to 2009.

2. STRUCTURE OF 2-AMINO-4*H*-PYRANS AND PHYSICOCHEMICAL PROPERTIES

2.1 Appearance

Most of the 2-amino-4*H*-pyrans are colorless, pale-yellow, or pale-cream crystals with high melting points. They are readily soluble in aromatic hydrocarbons, alcohols, acetone, acetonitrile, chloroform, DMF, and DMSO, and nearly insoluble in hexane and water.

2.2 Computational studies

Structure optimizations of several aminopyran molecules by semiempirical [PM3 (02T953), AM1 (02T953, 06AXCO705) and *ab initio* (HF/6-31G*) (02T953), HF/6-311^{++}G(d,p) (06AXCO705)] methods were applied to conformational analysis. Calculations predict the conformation of the pyran ring to be a considerably flattened boat, where O and C4 atoms are out of the plane and a substituent in position 4 adopts a pseudoaxial orientation. Atropoisomerism around the C4–C(Ar) bond has been studied (02T953). Thus, the energies of *syn*- and *anti*-periplanar atropoisomers for *o*-nitrophenyl-substituted pyran **3** are similar (difference 0.2–0.7 kcal/mol).

3 *ap*   **3** *sp*
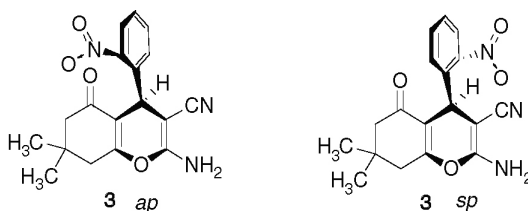
Rotation of a carbonyl substituent at C5 around the C5–C(=O) bond in pyrans **4** has been investigated by AM1 (06AXCO705). For 5-acetylpyran (R = Me) the most stable conformer is close to a *syn*-form (the torsion angle C6–C5–C=O is about 38° relatively to the flat conformation), whereas angles of 90 and 180° relative to the "boat bottom" plane correspond to maxima 2.2 and 4.1 kcal/mol, respectively. In the case of 5-benzoylpyran (R = Ph) the situation is the opposite. Minima, close in energy, are observed at 54 and −119°. Maxima at −38° (3.26 kcal/mol) and 176° (4.04 kcal/mol) correspond to steric interactions of the benzoyl Ph with C4–Ph and C6–Me. These data are in agreement with X-ray analysis (06AXCO705).

R = Me, Ph **4**
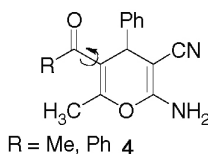
DFT calculations (B3LYP/6-31G*) for **5** have shown that the 2-amino tautomer is the most stable, and is lower energetically by 16.2 kcal/mol in comparison to its dinitrile precursor **6** (03T3753).

5   **6**
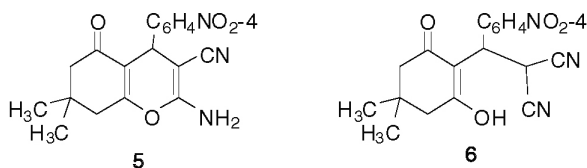
2.3 X-ray structural analysis

The X-ray data on molecular structure of 2-amino-4*H*-pyrans are consistent with computational data (86JOU1185, 87JOU369, 91CHE166, 92TL3809, 93T7133, 93TL5627, 94TA1435, 94TL3509, 95TA255, 96JHC27, 96RCB1945, 01AXC616, 02CHE1180, 02JFC63, 02RCB2238, 02T953, 03AXCO38, 03RCB1164, 04AXCO559, 04SC1425, 05AXCO741, 05JCX243, 06AXCO705, 07AXCO685). Thus, the pyran ring possesses the conformation of a flattened boat, where O and C4 atoms extend from the "bottom" by typical values of 0.097 and 0.221 Å (86JOU1185), 0.066 and 0.189 Å (96RCB1945), 0.179 and 0.341 Å (01AXC616), respectively. The most bulky 4-aryl substituent adopts a pseudoaxial orientation.

The plane of an aryl substituent is orthogonal to the "bottom of the boat" C2C3C5C6. The amino group is conjugated with the C2=C3 double bond, which is verified by shortening of the N–C2 bond [1.331 Å (86JOU1185), 1.336 Å (96RCB1945), 1.333 Å (01AXC616), relative to the standard value – 1.426 Å (86JOU1185)] and lengthening of the C2=C3 bond [1.359 Å (86JOU1185), 1.352 Å (96RCB1945), 1.356 Å (01AXC616), whereas the standard value is 1.333 Å (86JOU1185)]. The carbonyl group in 3-COOR-substituted pyrans forms an intramolecular hydrogen bond with the amino group proton (91CHE166).

In pyrans **7** with a bulky naphthyl substituent at C4, bond C4–C1′ ($C_{10}H_7$) are considerably elongated (1.540 Å), and the aryl plane is orthogonal to the pyran ring. A carbonyl group at C5 adopts a *syn-* or *anti*-conformation, as a rule, depending on substituent volume (04AXCO559, 07AXCO685).

7

R = Me, OEt   R = OMe, OPr-*i*,
                     OCH$_2$CH$_2$OMe, OBu-*t*
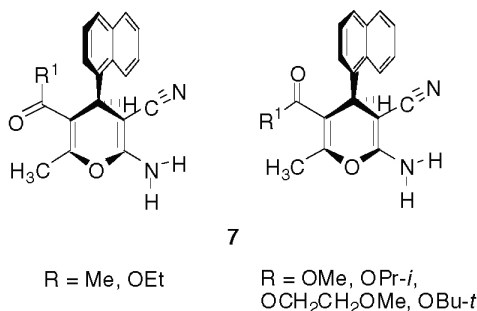
The absolute configuration at C4 of a series of enantiomerically pure nonannulated pyrans has been studied by X-ray analysis (92TL3809, 93T7133, 93TL5627, 94TA1435, 94TL3509, 95TA255).

In the case of 5,6,7,8-tetrahydrochromenes of type **8–10** the conformation of the pyran ring still is a flattened boat, while the cyclohexane ring adopts a semichair conformation (86JOU1185, 02T953, 03AXCO38, 03RCB1164, 04AXCO334, 05AXCO741). When tetrahydrochromenes possess a COOR (86JOU1185) or an NO$_2$ group (05AXCO741) in position 3, an intramolecular hydrogen bond N–H ··· O=C forms a six-membered ring. Intermolecular bonds NH ··· O=C5, NH ··· N≡C–C3 unite the molecules into infinite chains (86JOU1185, 03AXCO38, 04AXCO334, 05AXCO741, 05JCX243) or dimers (03RCB1164). Atropoisomerism was also studied on tetrahydrochromenes. Thus, **8** in the solid state exists as a mixture of *ap*- and *sp*-conformers in a 1:2 relation. Each aminopyran **9** exists in crystals as a single atropoisomer – *ap* **9a** (02T953), *sp* **9b** (03RCB1164).

8 - *ap*

8 - *sp*

9a, b

9a R = Me, Z = CN *ap*
9b R = H, Z = COOCH$_2$CH$_2$OMe *sp*
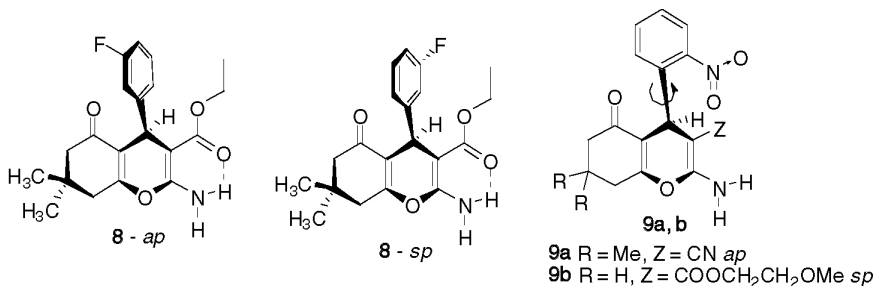
Structural features of 8-arylidene **10** (04SC1425) are comparable to those of **9b**, whereas double bond C8=CH(C$_6$H$_4$Cl-2) has an *E*-configuration.

10
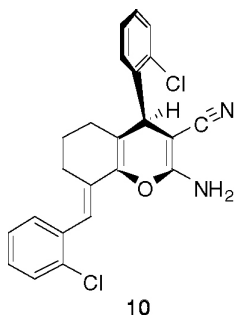
Structural studies of 2-amino-4*H*-naphtho[2,1-*b*]pyrans (87JOU369, 02RCB2238) and enantiomerically pure naphtha[1,2-*b*]pyrans (96JHC27) revealed a similarity in structural properties to those of **8** and **9**.

Studies of 6-aminopyranopyrazoles **11** (02CHE1180) show that they always exist in the crystal phase as a 2*H* (**11a**), instead of a 1*H*-tautomer (**11b**), as considered earlier. Molecules are joined into dimers by H-bonds, $NH_2 \cdots N1$, which, in turn, form ribbons as the result of inter-molecular binding of the N(2)H and N≡C groups. Pyrazole and pyran rings together (except for O and C4) are planar (dihedral angle is as low as 1.6°).

11a 2*H*   **11b** 1*H*
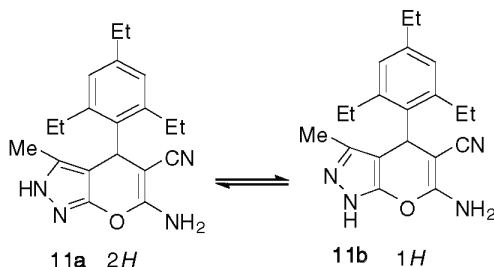
By contrast, N1-substituted pyranopyrazoles exist as "immobilized" 1*H*-tautomers (02JFC63).

Structural data were also obtained for spiro-conjugated 2-aminopyrans (09UP1). In **12** pyran, the ring adopts a flattened boat conformation: 1 and C4 reside out of the C2C3C5C6 plane (plane accuracy ±0.011 Å) by 0.070 and 0.146 Å, respectively. Bends in the heterocycle by lines C1 ⋯ C4, C2 ⋯ C6, and C3 ⋯ C5 are rather small: 10.0, 5.9, and 9.5°, respectively. The indoline portion is orthogonal to the plane of the "boat bottom" (dihedral angle 89.9°). Spiro-conjugation causes steric strain and leads to considerable elongation of the C–C bonds at C4.

12
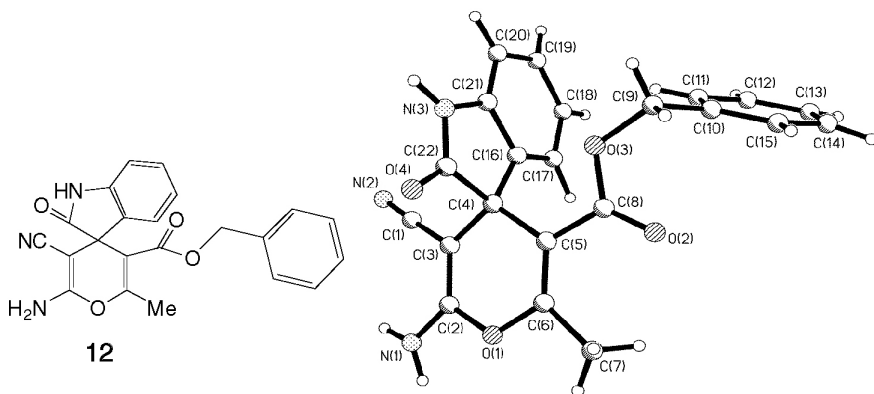
2.4 UV spectroscopy

UV spectroscopy is used as a supplementary method for characterization of 2-aminopyrans. Absorption bands in the 200–300 nm region are given by authors (70CJC3064, 78JHC57, 83CCC3123, 94H(38)399) without reference, and most correspond to $\pi \rightarrow \pi^*$ and $\pi \rightarrow n$ electron transfers of C=C–O and C=C–N fragments, as well as to $\pi \rightarrow \pi^*$ transfers of aryl substituents. Compounds **13** reveal a single absorption maximum at 296–305 nm (78JHC57), more recently (83CCC3123) at 206, 243, and 297 nm (when X = CN), and 208, 265, and 298 nm (when = COOMe).

R^1

NC — X

R^2 O NH$_2$
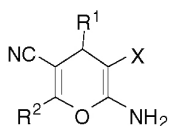
13

X = CN, CO$_2$Et; R^1, R^2 = Ph, 4-HOC$_6$H$_4$, 4-ClC$_6$H$_4$,
4-O$_2$NC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, 4-PhC$_6$H$_4$

Single maxima at 225–230 nm characterize 2-amino-4*H*-naphtho[2,1-*b*] pyrans (94H(38)399). Tetrahydrochromene **14** shows maxima at 220 and 269 nm (70CJC3064).

Me Me

CN

Me   O NH$_2$
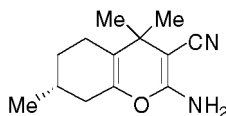
14

2.5 IR spectroscopy

Stretching vibrations of an NH$_2$ group (3450–3200 cm^{-1}) are always present in IR spectra of 2-amino-4*H*-pyrans (70CJC3064, 78JHC57, 83CCC3123, 86ZOR1315, 87JOU369, 91CHE166, 92TL3809, 93T7133, 93TL5627, 94H(38)399, 94TA1435, 94TL3509, 95T5901, 95TA255, 96JHC27, 96RCB1945, 01AXC616, 02CHE1180, 02JFC63, 02RCB2238, 03AXCO38, 03RCB1164, 04AXCO559, 04SC1425, 05AXCO741, 05JCX243, 06AXCO705, 07AXCO685, 08JCO364). Special analysis of IR and Raman spectra on a series of nonannulated pyrans has been carried out (87MI1). One or several bands in the 1650–1590 cm^{-1} region, attributed to bending vibrations of NH$_2$ and stretching

vibrations of C=C, are also characteristic for aminopyrans. More probably, these bands correspond to the superposition of $\delta(NH_2)$ and $\nu(C=C)$ vibrations. A general feature of 3-cyanopyrans is the presence of a highly intense stretching band of the C≡N group (2205–2180 cm^{-1}). The very high intensity and low-frequency shift possibly can be connected with a developed system of electron p–π-conjugation in an enamino nitrile moiety.
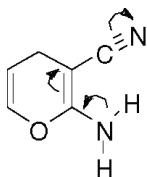
Notably, starting and intermediate nitriles used in the synthesis of 2-amino-3-cyanopyrans show moderate to weak nitrile group absorption at 2260–2220 cm^{-1}, the nitrile band is very characteristic.

Analogously, the ester C=O frequency in position 3 (86JOU1185, 87JOU369) is considerably lowered to 1690–1680 cm^{-1}, possibly due to conjugation with a C=C bond, as well as with the formation of an intramolecular hydrogen bond with the NH_2 group.

2.6 NMR spectroscopy

NMR spectroscopy is the main method for characterization of 2-amino-4H-pyrans. Most ^{1}H NMR data were obtained using DMSO-d$_6$ and CDCl$_3$. The spectra always contain a signal for NH_2 protons (br. s, 2H), but its chemical shift strongly depends on the nature of a 3-substituent and conditions (Table 1).

The majority of known 2-aminopyrans contain a single alkyl or aryl substituent R^1. So 4H reveals its very characteristic signal at 4.10–4.60 ppm. When R^1 is an aryl group with strong electron-withdrawing substituent in o- or m-positions, the 4H proton singlet shifts downfield to 4.50–5.50 ppm. When R^1 is 2-$O_2NC_6H_4$, a weak intramolecular hydrogen bond forms (03RCB1164). A small series of 6-unsubstituted 2-aminopyrans reveal an H(6) peak in the region 7.15–7.91 ppm in DMSO-d$_6$ (87CCC2687, 01T5591).

Investigations of internal rotation of a bulky R^1 using ^{1}H NMR (02CHE1180) at 20 and 60°C for **15a,b** in DMSO-d$_6$ show equal splitting of the protons of the phenyl ring and substituents, which indicates that sp- and ap-atropoisomers exist simultaneously in solution. However, at 120°C

Table 1. Chemical shifts of NH$_2$ protons
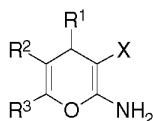
R^1 = Alk, Ar; R^2 = Ar, COR, CO$_2$R, CN; R^3 = Alk, Ar; X = CN, CO$_2$R

Substituent X	Solvent	Chemical shift (ppm)	References
CN	CDCl$_3$	4.50–4.82	78JHC57, 95T5901
	DMSO-d$_6$	6.50–7.50	96RCB1945, 02CHE1180, 02T953, 06AXCO705, etc.
CO$_2$R	CDCl$_3$	6.20–6.30	78JHC57
	DMSO-d$_6$	6.50–7.50	86JOU1185, 01AXC616, 05AXCO741

the rotational barrier is overcome and coalescence shows rapid rotation of the aryl group.

15a,b - sp   15a,b - ap

R = NO$_2$ (**a**), CH$_2$OEt (**b**)
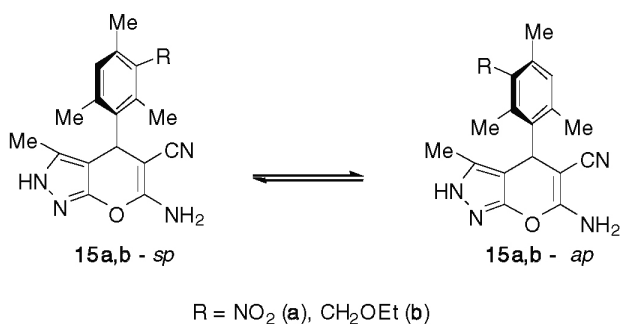
NMR spectroscopy on ^{13}C nuclei in 2-aminopyrans, in many cases, fail to report ^{13}C shifts with a reference, or are assigned inaccurately (86H(24)935). Some examples of chemical shifts and references are given below; the data for pyran **19** have been proven by the COSY technique (02T953). One paper (85MI2) was devoted to a comparative analysis of the spectra of pyrans **16**, **17**, as well as of those of a 2,6-dimethyl-4H-pyran analog.

16

86M247

17

86M247

18

90CCC718

19

02T953

20

89CB1323
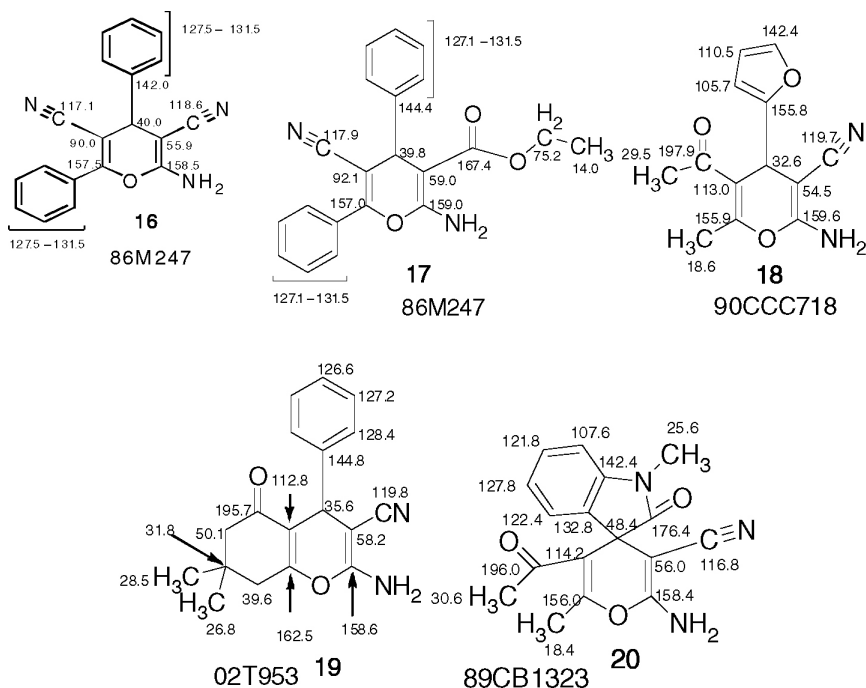
These spectral data reveal the following general features: C2 and C6 peaks are shifted downfield (158–162 ppm) relatively to ethylene [128.5 ppm (88MI1)], and C5 and especially C3 peaks are upfield due to p–π-conjugation with the lone pairs of O and N (for C3 only). A C4 signal is observed at δ 32–48 ppm. Carbon C1' of a 4-aryl or hetaryl group is slightly shifted downfield (132–156 ppm).

2.7 Mass spectrometry

Molecular ion peaks are commonly observed in EI mass spectra of 2-amino-4H-pyrans. Possible fragmentation pathways are shown in Scheme 1 (83CCC3123) on nonannulated pyran **21**. A peak due to a retro-Michael cleavage product (m/z 309, elimination of malononitrile) is observed. The unsaturated cyanoketone undergoes subsequent deacylation with ions m/z 181, 128. Another pathway involves elimination of a phenyl radical with aromatization to a pyrillium cation (m/z 298). Notably, efforts to isolate similar pyrillium cations failed (86JPR35), possibly due to the destabilizing action of nitrile groups on the resultant
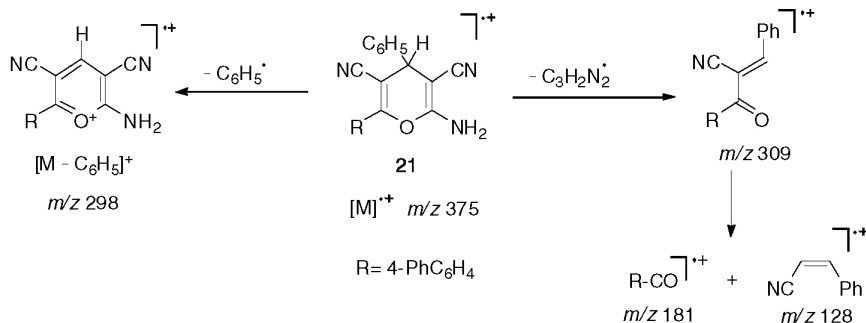
Scheme 1

electron-deficient heterocycle. Elimination of an aryl radical has been also observed in (02T953) (Scheme 1).

3. METHODS OF SYNTHESIS

The most widely known 2-amino-4H-pyrans contain a primary amino group, generalized in **22**. The general synthetic approach involves cyclization of Michael adducts **23** (or **6** as a particular example) via nucleophilic addition of an enolic oxygen to a nitrile group and subsequent tautomeric shift of the resultant 2-iminopyran to 2-aminopyran. Acyclic intermediates **23** can be generated (usually, without isolation) from appropriate Michael donors and acceptors: methylene-active carbonyl compounds **24** and unsaturated nitriles (UN) **25** (Method 1), or from α,β-unsaturated carbonyl compounds (UCCs) **26** and CH-acidic nitriles **27** (Method 2) (Figure 1). A three-component synthesis, involving direct reaction of methylene-active carbonyl compounds **24**, aldehydes **28** or cyclic ketones **29** and nitriles **27**, is very convenient because intermediates **25** and **26** are generated *in situ*. A wide series of carbonyl compounds, their hidden forms, carbo- and heterocyclic ketones, as well as phenols, can serve as **24**, opening pathways toward various substituted and annulated aminopyrans (Figure 1).

3.1 Synthesis of nonannulated 2-amino-4H-pyrans

For the synthesis of nonannulated 2-amino-4H-pyrans, acyclic carbonyl compounds **24** are used in Methods 1, 2, and 3. Generally, readily accessible ketones **24**, as well as unsaturated nitriles **25** contain electron-withdrawing substituents (R^1, X). Consequently, densely functionalized pyrans **22** are formed. UNs, widely used for aminopyran preparation, include **30–34**

Method

(1)

(2)

(3)

R^1–R^4 = H, alkyl, aryl, cycle, CN, COOR
X = CN **(a)**, COOR **(b)**, NO$_2$ **(c)**

28 (R^3=Alk, Ar; R^4=H),
29 (R^3+R^4=cycle)
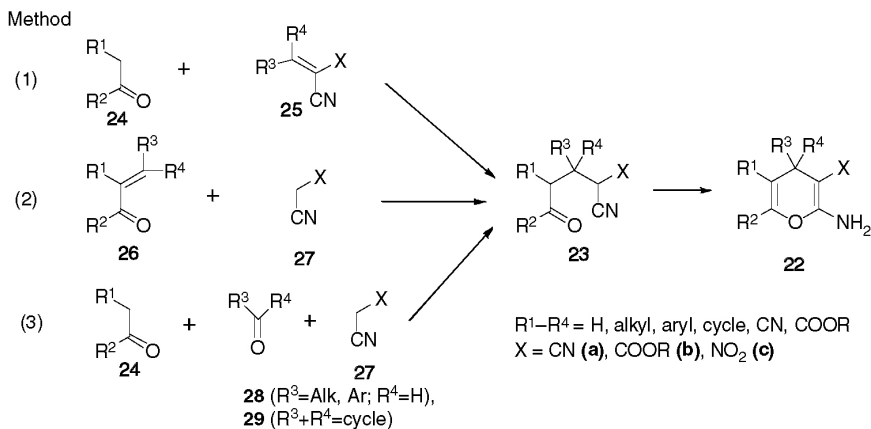
Figure 1 General methods of 2-amino-4H-pyran synthesis.

(Figure 2). β-Diketones **35** and β-ketoesters **36–38** are commonly used as CH-acidic ketones **24**. Cyanoketones **39** and **40**, nitroketones **41**, as well as ketones substituted with heteroaromatic **42**, sulfur-containing **43**, and phosphorus-containing groups **44** and **45** are also favored (Figure 2). Syntheses

Unsaturated nitriles

Methylene-active carbonyl compounds

R^1 = Alk; R^2 = Alk, Ar; R^3 = Ph, OAlk
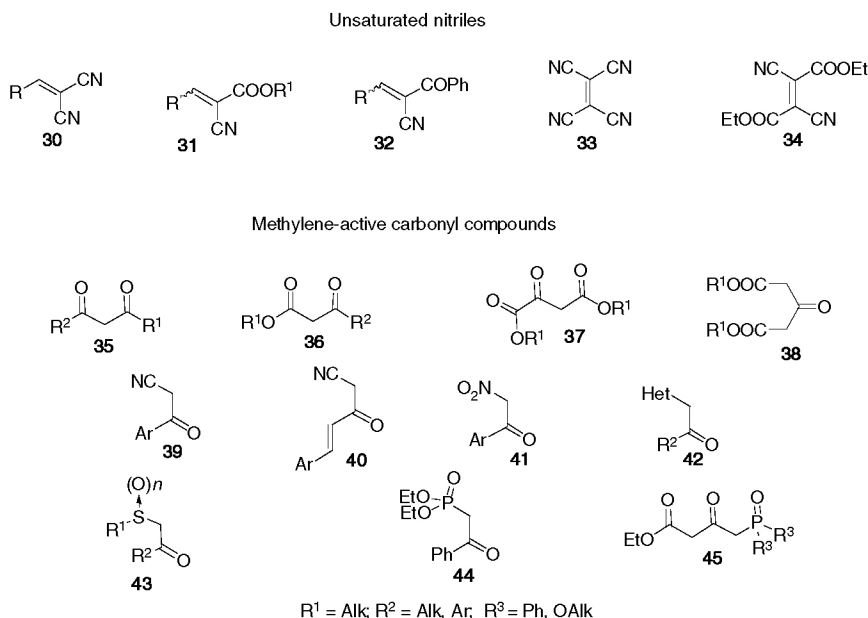
Figure 2 Widely used starting materials for Method 1.

Ar = Ph, 3-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-C$_4$H$_3$O, 2-C$_4$H$_3$S; X = CN, COPh
R = Me, Ph

Ar = Ph, 3-BrC$_6$H$_4$, 2-C$_4$H$_3$O, 2-(4-Br)C$_4$H$_3$O, 2-(4-NO$_2$)C$_4$H$_3$O,
2-(4-Ph)C$_4$H$_3$O, 2-(4-(4-MeO)C$_6$H$_4$)C$_4$H$_3$O; X = CN, CO$_2$R
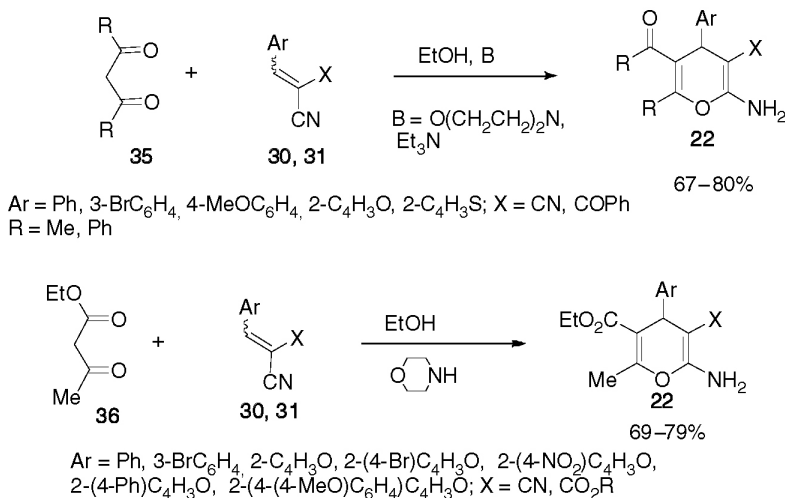
Scheme 2

are easily carried out on heating in ethanol with basic catalysts, such as triethylamine, morpholine, piperidine, and more rarely with EtONa.

Scheme 2 gives generalized examples of interaction of UNs **30** and **31** with dicarbonyl compounds **35** (82ZOR625, 86H(24)935, 87H(26)2811, 90IJB322, 90IJB1020) and **36** (82ZOR625, 83ZOR164, 84JHC1261, 86H(24) 935, 89LA585) (Method 1).

Application of 4-chloroacetic ester **46** (89CCC1336, 03RCB2185, 06S2357) opens access to 6-chloromethylpyrans **47**, which are useful for further chemical transformations (e.g., into condensed aminopyrans) due to the presence of the labile chlorine atom (Scheme 3).

Syntheses with oxaloacetic esters **37** (80ZOR2188) and acetonedicarbonic esters **38** (03S227) lead to pyran-dicarbonic esters **48** with moderate to high yields (Scheme 4).

Utilization of fluoroalkyl-substituted dicarbonyl compounds is accompanied with side reactions. Trifluoro diketone **49** undergoes an acidic Claisen cleavage in ethanol with formation of dicyanoketone **50**, which
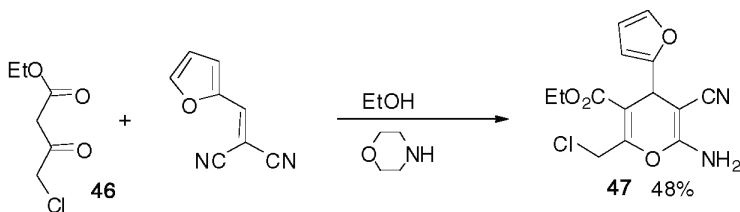
Scheme 3
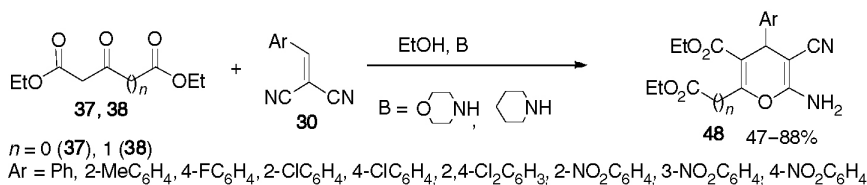
Scheme 4

does not transform to an aminopyran (82JOU544). 3-Cyanopyridone-2(1) **51** is also formed, and its structure has been proven by independent synthesis from thienoylacetone and malononitrile **27a** (MN). Michael adducts of chalcones and MN, similar to **50**, also do not undergo cyclization, possibly, due to their low degree of enolization. Application of strong bases such as RONa leads to competitive solvolysis of the cyano group, pyridones **51**. Another study on the reactivity of diphenyl analog of **50** has shown that it cannot form 2-aminopyran, although various carbo- and heterocycles can be obtained from it under certain conditions (91TL5375). So, 5-unsubstituted 2-aminopyrans are not readily accessible (Scheme 5).

Trifluoro acetoacetic ester **52** reacts with **30** yielding mixtures of ami- nodihydropyran **53** and piperidone **54** (06T2255) (Scheme 6).
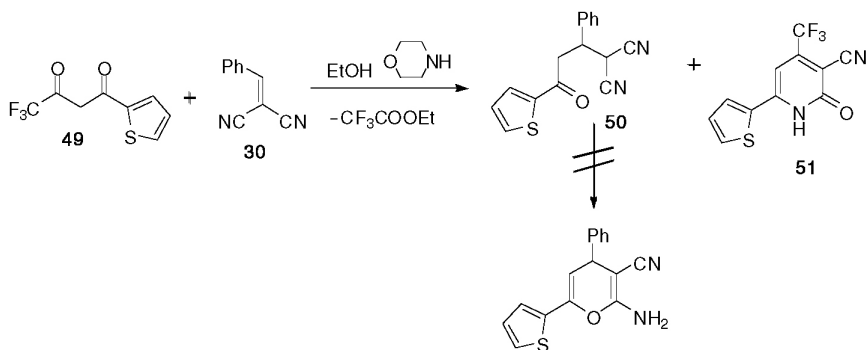
Scheme 5
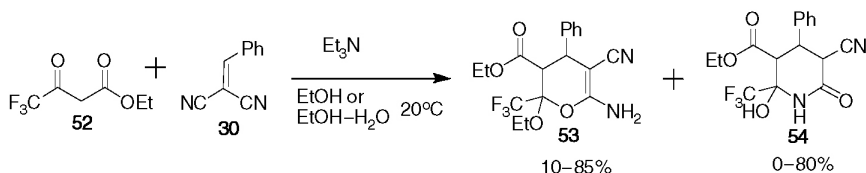
Scheme 6

The mixture composition depends strongly on the EtOH:H$_2$O ratio, while the highest yields of pyran have been achieved in absolutized ethanol. Formation of 6-ethoxydihydropyran **53** possibly can be attributed to the influence of the CF$_3$ group, which is a very strong acceptor and its presence in carbonyl compounds promotes acetal formation.

The reaction of tetracyanoethylene (TCE) **33** with acetylacetone **35** proceeds ambiguously without a catalyst when it depends on the solvent properties. Thus, in ethanol, a Michael adduct is formed as the only product, while acetonitrile promotes formation of pure aminopyran **55**. Furthermore, the Michael adduct, isolated from ethanol solution, cyclizes to pyran in acetonitrile in 48 h (74JP1595, 99RJO1693) (Scheme 7), whereas 2,3-dicyanofumaric ester forms Michael adducts, which do not transform to pyrans at all. The same pyran **55** has been synthesized by reaction of tetracyanodiacetylcyclopropane **56** with triarylphosphines (99RJO1693). Benzoylacetone, dibenzoylmethane, and aroylacetic esters react analogously to acetylacetone (74JP1595) (Scheme 7).

One of the modern trends in heterocyclic synthesis is illustrated by the synthesis of aminopyrans from UNs **30** and acetoacetic ester **36**, immobilized on a homogenic substrate – ionic liquid **57**, highly soluble in

R^1 = Me, Ph, OEt
R^2 = Me, Ph, 4-NO$_2$C$_6$H$_4$
Ar = Ph, 4-MeC6H4

Scheme 7

Ar = Ph, 4-HOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 3-BrC$_6$H$_4$, 4-HO-3-Me-C$_6$H$_3$

Scheme 8

Ar = Ph, 2-C$_4$H$_3$O, 2-C$_4$H$_3$S
X = CN, CO$_2$Et
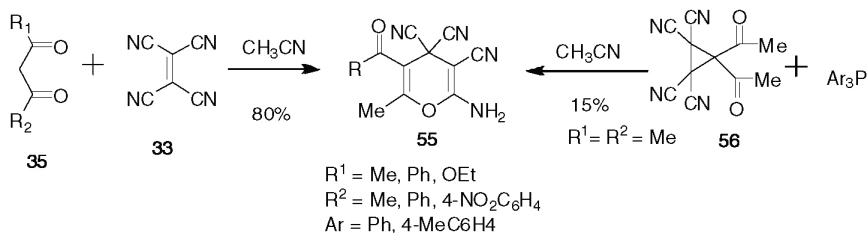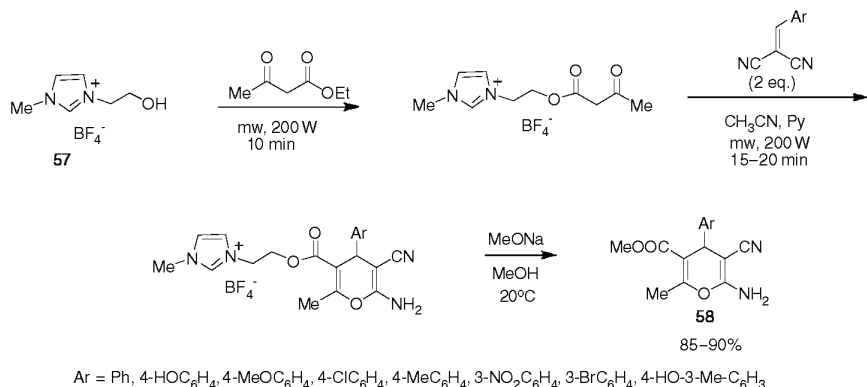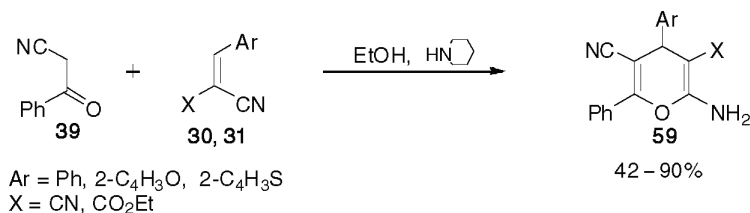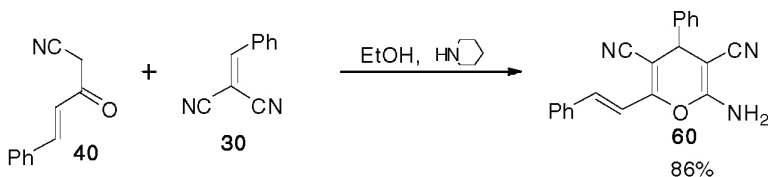
Scheme 9

Scheme 10

acetonitrile (05TL3031). Reesterification opens access to pyrans **58** (Scheme 8). The key stages are carried out on microwave heating, and the ionic liquid **57** can be regenerated after the workup.

Another modern modification involves coupling of UNs **30** and β-ketoesters **36** in aqueous emulsion in the presence of an interphase catalyst triethylbenzylammonium chloride (TEBAC) (06JCM228).

The nitrile group, similarly to a carbonyl, can serve as an activator for ketones in the syntheses of aminopyrans. Reaction of benzoylacetonitrile **39** with UNs **30** and **31** illustrates Method 1 (83LA1468, 86M247) (Scheme 9).

Unsaturated cyanoketone **40** forms pyran **60** in reactions only with benzalmalononitrile **30**; cyanoester **31** gives complex mixtures (86M247) (Scheme 10).

Examples given earlier clearly indicate that various ketones possessing electon-withdrawing group (EWG) in an α-position can serve as Michael donors in Method 1. In particular, the EWG may be an acceptor group, containing nitrogen, sulfur, or phosphorus. Nitrogen heterocycles [azoles (95CHE1478, 96RCB1945), pyridine (02CHE251)] were employed as N-containing acceptors. *N*-Acetonyl- and *N*-phenacylazoles **42** yield 5-azolyl-substituted pyrans **61**, whereas the substitution pattern in azole nuclei does not affect the reaction course. Only the absence of steric constraints is essential (95CHE1478, 96RCB1945) (Scheme 11).

When a 4-pyridyl substituent was used as an acceptor, the yield of pyran **62** was moderate (02CHE251) (Scheme 12).

There is an example of the preparation of 2-amino-5-nitro-4*H*-pyrans **63** from aromatic α-nitroketone **41** and UNs **30** (98CHE1409) (Scheme 13).

Az $-$CH$_2-$C(=O)$-$R **42** + NC$-$C(Ar)=CH$-$CN **30** $\longrightarrow$ **61** 24–69%

Az=

R = Me, Ph

Ar = Ph, 3-IC$_6$H$_4$, 4-FC$_6$H$_4$, 2-C$_4$H$_3$S

Scheme 11

41 + **30** $\xrightarrow{\text{HN piperidine, EtOH}}$ **62** 45%

Scheme 12

41 + **30** $\xrightarrow{\text{CH}_3\text{CN, Et}_3\text{N}}$ **63** 40–60%

Ar = Ph, 2-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 2-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$
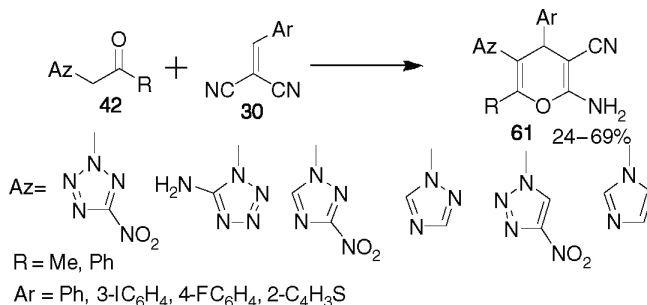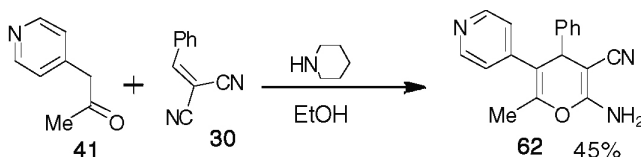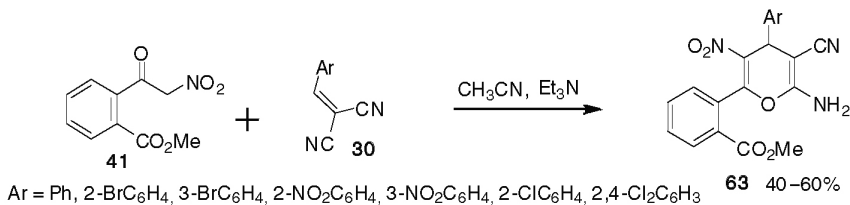
Scheme 13

However, this reaction possibly does not have a general character (e.g., unsubstituted α-nitroacetophenone does not react under the described conditions).

A synthetic approach toward diethylphosphonyl pyrans **64** and **65** was proposed based on the reaction of β-ketophosphonates **44** and **45** and UNs (99H(51)1137, 04PS2487). Noteworthy, in the case of the phosphonate **45** the reaction proceeds regioselectively with formation of 5-ethoxycarbonylpyran **65** only (Scheme 14).

The phosphonic group can be introduced in position 4 of a pyran ring (**66**) by utilization of phosphorus-containing UN **67** in a reaction with methylene-active ketones **35** or **36** on continuous heating in ethanol (00PS(165)17) (Scheme 15).

Sulfur-containing groups serve as acceptors successfully. β-Ketosulfoxides and β-ketosulfones **68** form aminopyrans **69** with UNs
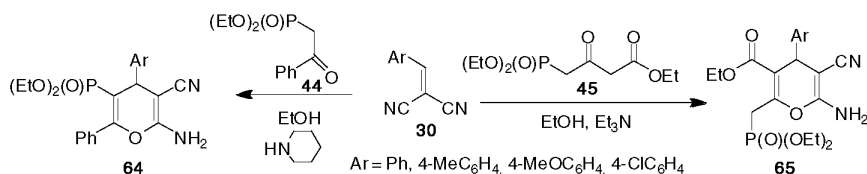
Scheme 14
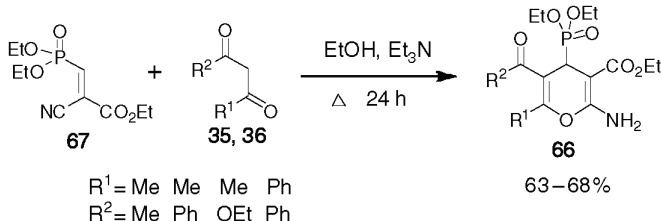
Scheme 15

30 and **31**. Noteworthy, employment of chiral β-ketosulfoxides leads to single stereoisomer formation due to asymmetric induction of the S $\rightarrow$ O group (95JOC6678, 97JOC6575) (Scheme 16).

Sulfur-containing substituents, in particular, 2-(3-cyanopyridil)thiomethyl fragments, can be introduced in position 6 of 2-aminopyrans via nucleophilic substitution reactions (03RCB2185, 06S2357). One approach consists in a preliminary synthesis of 4-substituted acetoacetic esters **70** from pyridinethiones **71** and chloroacetic esters **46**, with subsequent interaction of the latter with UNs **30**. The second approach involves the synthesis of 6-chloromethylpyrans **47** and their subsequent interaction with pyridinethiones **71** (Scheme 17). The yields of pyrans **72** in general vary from good to quantitative and do not depend much on the method used. Taking into account the diversity of accessible UNs **30** and pyridinethiones **71** (containing aliphatic and aromatic substituents; pyridines, condensed with carbocycles), it is notable that this methodology offers broad possibilities for combinatorial synthesis (Scheme 17).

Scheme 16

Ar = Ph, 2-IC$_6$H$_4$, 2-C$_4$H$_3$S, 4-EtC$_6$H$_4$, 3-(OCH$_2$Ph)C$_6$H$_4$, 3-BrC$_6$H$_4$,
2-(5-NO$_2$C$_4$H$_2$S), 3,5-(MeO)$_2$C$_6$H$_3$
R^1 = Me Me Me   4-ClC$_6$H$_4$ H   H   H
R^2 = H   Me H   H   -(CH$_2$)$_3$- -(CH$_2$)$_4$- -(CH$_2$)$_5$-
R^3 = OH Me Me   2-C$_4$H$_3$S
R^4 = Me, Et, *i*-Pr
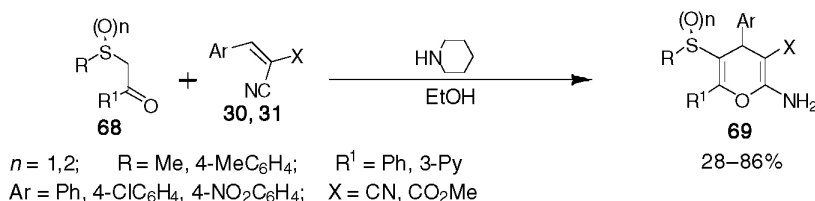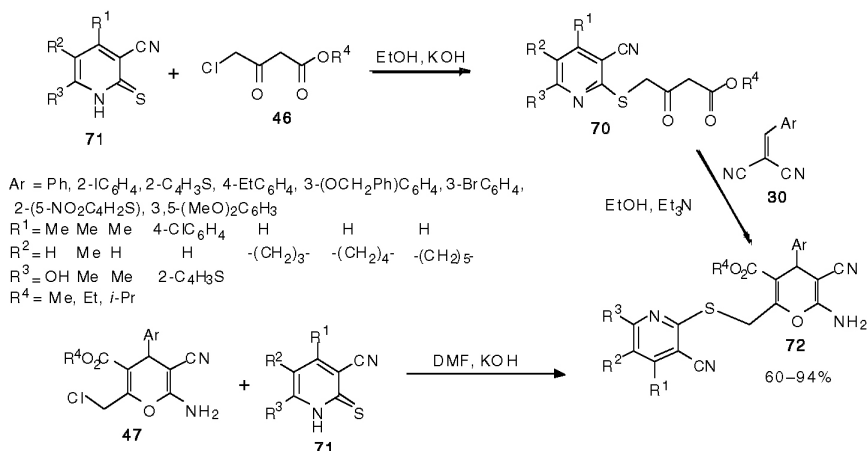
Scheme 17

There are some examples of pyran synthesis by Method 2, which involves the reactions of unsaturated ketones with methylene-active nitriles. In a typical case of Method 2, the Michael reaction of α,β-unsaturated carbonyl compounds **26** (77TL1835, 78JHC57, 83CCC3123, 90CCC718) with MN **27a** or cyanoacetic esters **27b** leads to pyrans **73** (Scheme 18).

2-Benzoyl-3-phenylacrilonitrile **26** (X = CN), which has found application in Method 1 (as a Michael donor), can show ambident reactivity (77TL1835, 78JHC57, 86H(24)935). This unsaturated ketonitrile, being a good Michael acceptor, is able to add to both carbonyl compounds **36** and cyanoacetic acid derivatives **27**. In the first case, Method 1 is performed (86H(24)935) and in the second – Method 2, respectively (77TL1835, 78JHC57) (Scheme 19).

In general, the procedures of Method 2 are similar to those of Method 1; however, in some cases (90CCC718) they are complicated by side reactions (e.g., exchange of methylene groups, leading to the formation of a UN).

Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-HOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 2-C$_4$H$_3$O
R = Me, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-C$_6$H$_5$C$_6$H$_4$
X = COMe, CO$_2$Me, CO$_2$Et, CO$_2$Pr-*i*, CN
Y = CN, CO$_2$Et
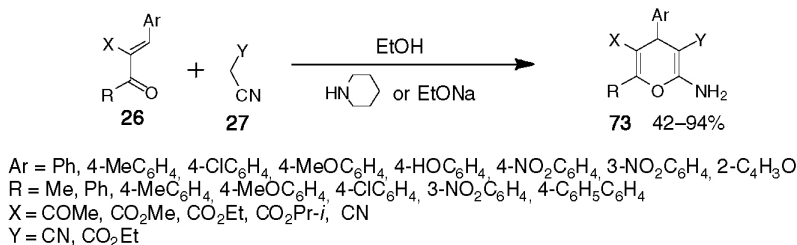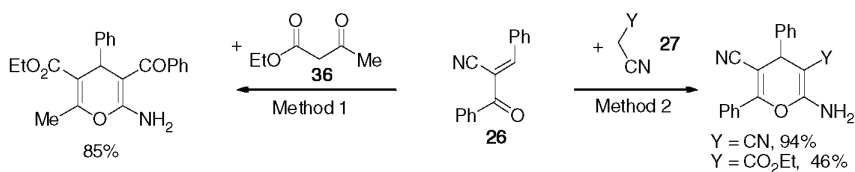
Scheme 18

Scheme 19

The paper 93LA801 demonstrates some advantages and disadvantages of Method 2. Attempts to obtain amides **74** by Method 1 failed. For the realization of Method 2, acetoacetic acid amides **75** have been introduced into a Knoevenagel condensation with benzaldehyde. The unsaturated ketoamides **76** formed have been reacted with MN **27a**. Finally, only one pyran **74** from the series has been isolated, the yield being very low (8%). Cinnamoic acid amide **77** was the only identified side product. Further studies have shown that for amides **76** the more preferred reaction pathway consists in a consecutive "Michael–Knoevenagel" condensation with 2 equiv. of MN, followed by Thorpe–Ziegler cyclization with formation of cyclohexadienes **78** (93LA801) (Scheme 20).

Most probably, the last stage in the synthesis of 2-amino-4*H*-pyrans involves base-catalyzed nucleophilic addition of the enolic oxygen to a C≡N group, which can be regarded as a "*hetero*-Thorpe–Ziegler" reaction (Scheme 21).
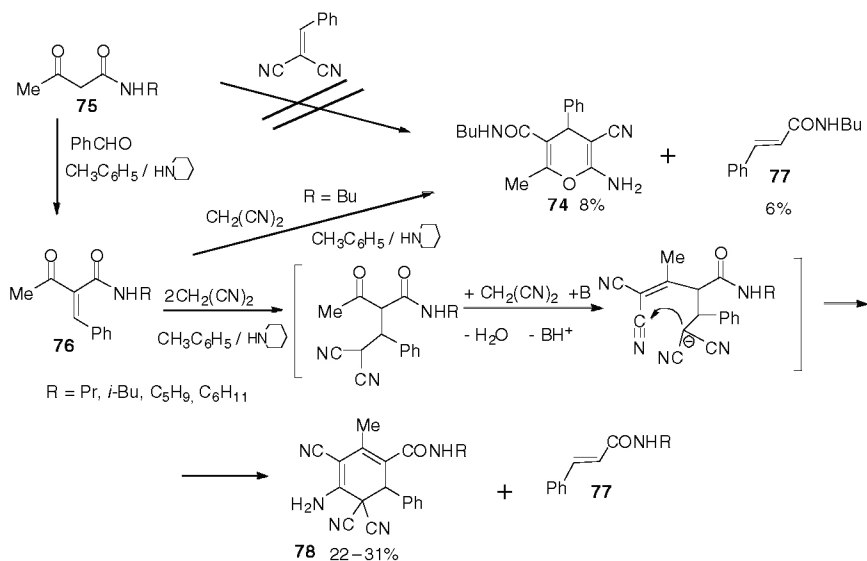
Scheme 20
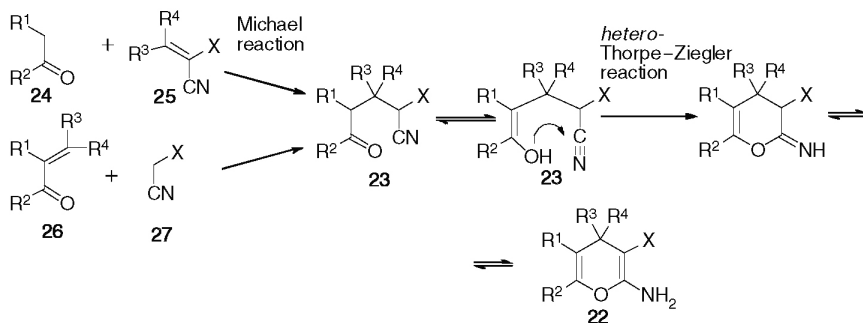
Scheme 21

If a C≡C bond is formally substituted for C≡N, the reaction could proceed analogously; however, it would require accessible aminoacetylenes. Reagents of this type exist (e.g., *N,N*-diethylpropin-1-amine **79**), and react with α,β-unsaturated ketones **26** without a catalyst in inert solvents (73JHC165). This is a convenient approach toward 2-*N,N*-dialkylamino-4*H*-pyrans **80** and **81**, which are formed, probably, via the *hetero*-Diels–Alder reaction (Scheme 22).

Reaction of methylene derivatives of malonic dialdehyde **82** with nitriles **27** leads to 6-unsubstituted aminopyrans **83** (87CCC2687, 01T5591) (Scheme 23).

A significant limitation, because of which only a few examples of 6-unsubstituted aminopyrans are known, is poor accessibility and lack of stability of starting materials **82** [generated, for example, via imminium salts (01T5591)].

For the synthesis of aminotriacetylpyrans **84** a reaction of 3-bromoacetylacetone **85** with cyanoacetic ester in ethanolic NaOH was employed. Possibly, it proceeds via the formation of acetylacetone dimer **86**

Scheme 22

82 + ZCH$_2$CN (27) →(Bu^{t}OH, Et$_3$N or EtOH, piperidine NH)→ 83   39–87%

Ar = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-C$_4$H$_3$S, Cl$_2$C=CH-CH=CH-;

Z = CN, CO$_2$Me
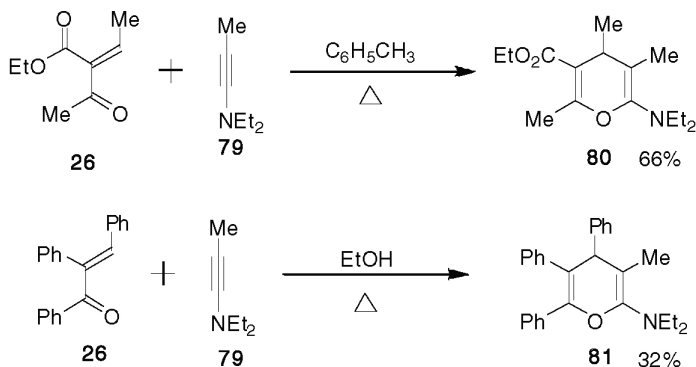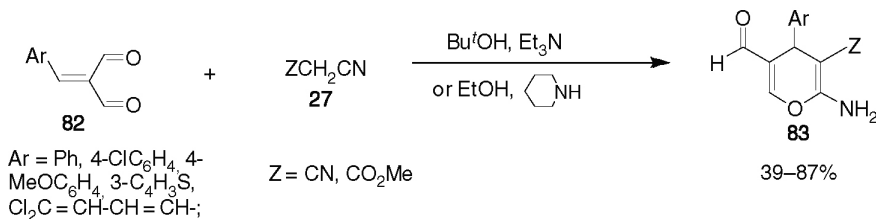
Scheme 23

(59ACS692). However, using suggested conditions the formation of 2-aminofurans **87** is predominant (Scheme 24).

Isoxazoles **88** can serve as a convenient masked form of aldehydes and ketones (84H(22)1, 85JCS(P1)2581). They can be cleaved by EtONa in the presence of aldehydes. The 3-oxonitriles, generated *in situ*, react as aldehydes with UCC **26** formation, followed by reaction with MN **27a** to give pyrans **89**. The yields are usually low, rarely reaching 60–76%, but the access to 6-unsubstituted pyrans should be regarded as the advantage of this method (Scheme 25).

Studies on sulfur-substituted 2-pyridones have shown (99M545) that unsaturated phenylthio ketones **90** can yield aminopyrans **91** with MN **27a**, while enaminone (X = NMe$_2$) gives 2-pyridones **92** (Scheme 26).

2-Amino-4-aryl-4*H*-pyrans contain an asymmetric carbon atom in position 4. Therefore, extensive efforts were undertaken to obtain
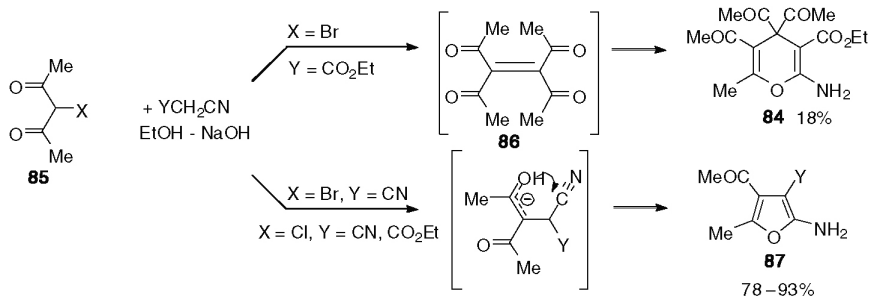
Scheme 24
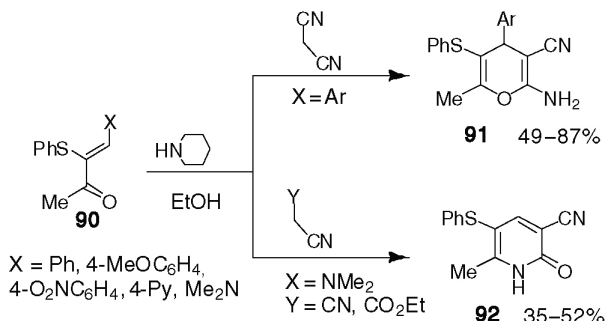
Scheme 26

enantiomerically pure aminopyrans (92TL3809, 93T7133, 93TL5627, 94T3509, 94TA1435, 95TA255). Stereoselective synthesis was conducted by introducing chiral auxiliaries into the starting compounds with subsequent separation of diastereomers and, if possible, cleavage of the auxiliary. To achieve this goal, both Methods 1 and 2 were employed; chiral auxiliaries were appended to either Michael donors or acceptors. Thus, chiral aldehydes (92TL3809, 93T7133), cyanoacetic acid derivatives (94TA1435, 95TA255), and β-ketoesters (93TL5627, 94T3509) were used.

The reaction of α,β-unsaturated ketones **93**, obtained from β-ketoesters **36** and chiral aldehydes **94** [derivatives of D-glyceral (92TL3809, 93T7133), and D-mannitol (93T7133)], with MN have been used for the first time in the synthesis of optically pure 2-aminopyrans **95**. Yields and diastereoselectivity were low; however, recrystallization afforded one of the stereoisomers in a nearly pure state (d.e. 80–100%) (Scheme 27).

Utilization of bases with different cations made it possible to obtain pyrans with predominantly either the 4-(R) (K, Na, $C_5H_{12}N^+$) or the 4-(S) (Li, Mg) isomer.

A series of cyanoacetic acid derivatives **96** (94TA1435, 95TA255) was used for the introduction of a chiral moiety into position 3 of a pyran ring: Oppolzer's sultam (a), (−)-menthol (b), (1S)-endo-(−)-borneol (c), ethyl (S)-(−)-lactate (d), diisopropylidene-D-glucofuranose (e). Both Methods 1 and
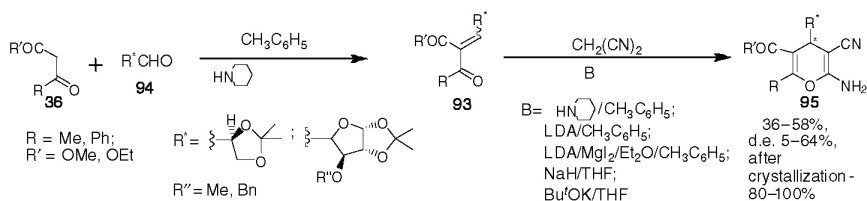
Scheme 27

2 were investigated. The authors failed to obtain pyran (a) with group (a), but all the other pyrans **97** were synthesized in good yields and moderate diasteromeric excess after flash chromatography. Independent of the method applied, in all cases predominant isomer possessed the (4S)-configuration. Recrystallization afforded pure isomers with borneolic (c) and lactate (d) moieties. Numerous attempts to cleave the menthyl substituent (hydrolysis, reesterification, reduction) failed and led to the decomposition of the pyran ring (Scheme 28).

Finally, chiral acetoacetic esters **99** were used in the synthesis of pyrans **98** (93TL5627, 94T3509). In cases a–c both Methods 1 and 2 led to pyrans **98** with a low degree of diastereoselsctivity (Scheme 29).

On the contrary, application of Oppolzer's chiral sultam **100** in Method 1 led to good diastereoselectivity (d.e. 60–70% after chromatography), and pure (4R)-diastereomers have been isolated by recrystallization. Moreover, the chiral auxiliary was cleaved successfully by reduction with LiAlH$_4$. 2-Aminopyran-5-carbinols **101** were produced without
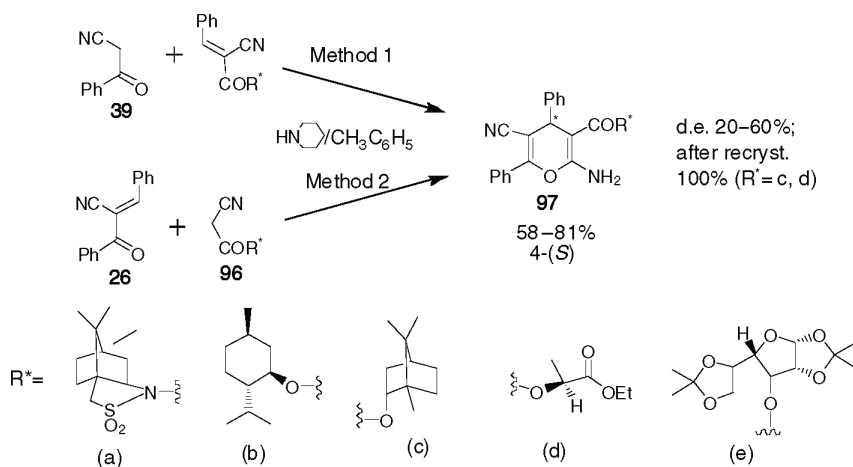
Scheme 28
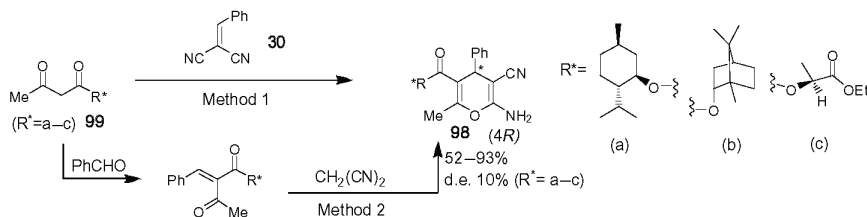
Scheme 29
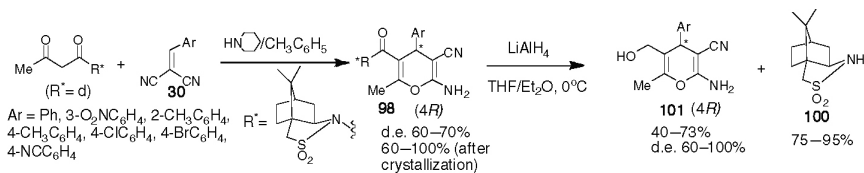
Scheme 30

racemization pure or enriched, depending on the d.e. of the starting **98**. At the same time sulfamide **100** was regenerated in high yields (94T3509) (Scheme 30).

The Methods 1 and 2 are well developed and afford broad potential in the synthesis of 2-aminopyrans. However, recent years are marked with the rapid development of multicomponent (three-component) Method 3, in which carbonyl compounds **24**, **28**, and nitriles **27** are mixed together simultaneously to generate the Michael acceptor *in situ* and subsequent cyclization in one synthetic stage. Significant advantages of Method 3 consist in reducing the number of synthetic stages, which often involve laborous workup, and elimination of the necessity to work with unsaturated nitriles **30** and **31**, which are in many cases toxic and lacrimatory agents. One of the first examples of Method 3 involved electogeneration of a base (99H(51)1101). The method was characterized by high yields and simple design of the electrolytic setup (Scheme 31).

Multicomponent reactions of this type, in the concepts of Tietze, who introduced the term "domino reactions" (96CRV115), can also be regarded as "domino reactions" of the type: "Knoevenagel–Michael–*hetero*-Thorpe–Ziegler" in accordance with the probable mechanistic scheme (Scheme 32).

The experimental simplicity of Method 3 has attracted the specialists in modern trends in catalysis. Thus, in Method 3 different authors used RbF (04SC4431), MgO (09EJM3805), KF/Al$_2$O$_3$, mixed magnesium-aluminum carbonate, or mixed magnesium-lanthanum oxide (08TL2730) in methanol. Recently, 2-aminopyran syntheses with acetylacetone **35** and ethyl acetoacetate **36** were carried out in an ionic liquid [(bmim)(BF$_4$), 1-butyl-3-methylimidazolium borofluoride] with 1,1,3,3-tetramethylguanidine as
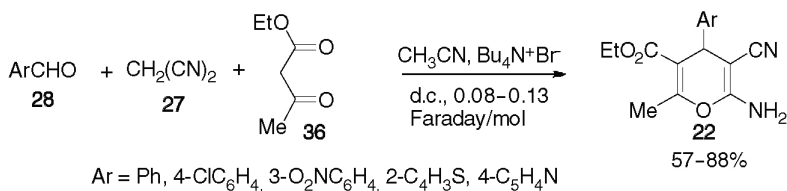
Scheme 31
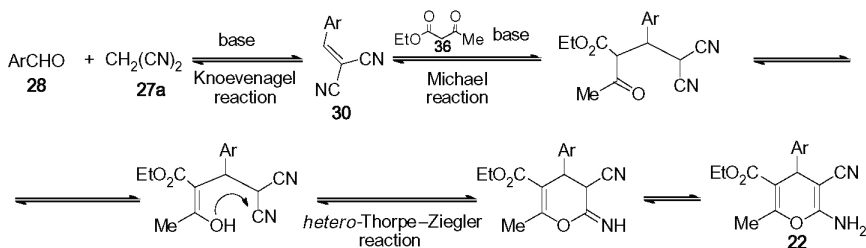
Scheme 32

catalyst (05M727). The paper (05SC1381) describes a three-component synthesis of aminopyrans from aromatic aldehydes, MN **27a**, and acetoacetic ester **102**, grafted to a soluble polymer support – polyethylene glycol (PEG). Ester **102** was synthesized from 2,2,6-trimethyl-4H-1,3-dioxyn-4-one with PEG in toluene under microwave irradiation (Scheme 33).

Three-component Method 3 was utilized in the synthesis of pyrans with 6-(2-pyridyl)thiomethyl substituents (03RCB2185, 06S2357), in addition to Method 1.

In concluding this current section, let compare Methods 1–3 in the synthesis of 2-amino-4H-pyrans. In Table 2 are given the yields of pyrans, obtained by Methods 1–3, as well as diastereomeric excesses in some cases. Seven examples show that in each case one of the three methods can give a higher or lower yield, but in general, all the methods produce 2-aminopyrans in good to quantitative yields. Thus, the method of choice should be found experimentally in each case. Other things being equal, Method 3 is the simplest because it proceeds only in one synthetic stage.

PEG = -[CH₂CH₂O]ₙH
Ar = Ph, 4-MeOC₆H₄, 4-ClC₆H₄, 2-ClC₆H₄, 2,6-Cl₂C₆H₃, 2,4-Cl₂C₆H₃, 4-FC₆H₄, 3-NO₂C₆H₄, 3-BrC₆H₄, 4-HOC₆H₄, 3,4-OCH₂OC₆H₃
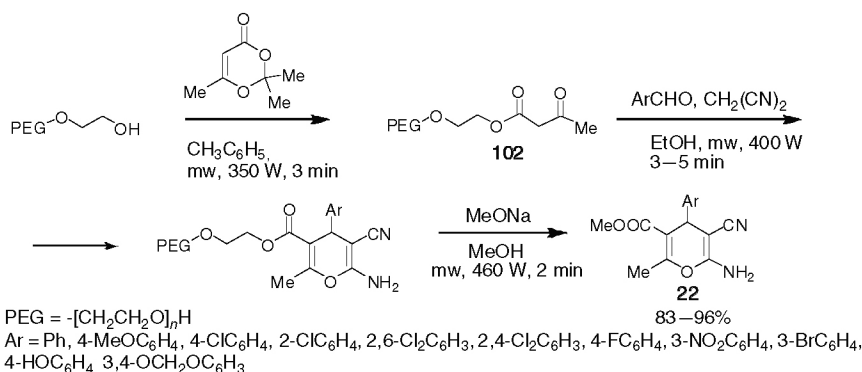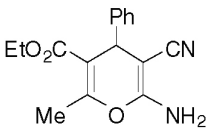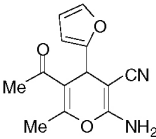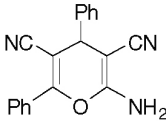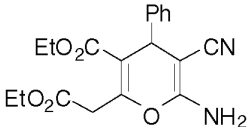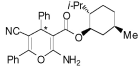
Scheme 33

3.2 Synthesis of 2-amino-4*H*-pyrans, annulated with five- to seven-membered carbocycles

As with the nonannulated aminopyrans, general Methods 1–3 have found application in the synthesis of carbo-annulated aminopyrans.
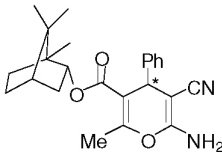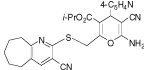
Among the reactions of the first type, the interactions of substituted 1,3-cyclohexanediones **103a–c** with various UNs (82JOU544), including cya-nonitroalkenes **25c** (84ZOR2481), are the most developed. Probably, due to

Table 2. Comparative characterization of the Methods 1–3: yields and d.e. of 2-amino-4*H*-pyrans

Compound	Method 1 yield/reference	Method 2 yield/reference	Method 3 yield/reference
	80/(86H(24)935) 60/(84JHC1261)	87/(84H(22)1)	75/(99H(51)1101) 68/(04SC4431) 83/(08TL2730)
		82/(90CCC718)	70/(90CCC718)
	–	90/(86M247)	91/(78JHC57)
	81/(03S227)	–	89/(04SC4431)
	72, d.e. 20% (95TA255)	81, d.e. 20% (95TA255)	–

Table 2 *(continued)*

Compound	Method 1 yield/reference	Method 2 yield/reference	Method 3 yield/reference
	94, d.e. 10% (94TA1435)	59, d.e. 10% (94TA1435)	–
	67/(06S2357)	–	48/(06S2357)

the high degree of enolization of 1,3-cyclohexanediones, formation of 5,6,7,8-tetrahydrobenzo[*b*]pyrans **104** (5,6,7,8-tetrahydrochromenes) proceeds rapidly and leads to high yields (Scheme 34).

These reactions are carried out in acetonitrile (74JCS(P1)2595) or alcoholic solutions in the presence of an organic base (70ZNB1423, 82JOU544, 83JOU150, 86JOU1185, 89JPR971, 03RCB1164), with heating or at ambient temperature, as well as in DMF with KF–Al$_2$O$_3$ (03SC119), or without a solvent under microwave irradiation (02SC2137).

Syntheses of pyrans **105** from phosphonic unsaturated nitrile **106** require continuous reflux (00PS(165)17) (Scheme 35).

Tetrahydrochromenes **107**, containing perfluoroalkyl and phosphonic groups in the same molecule, have been obtained via the interaction of dimedone **103b** with nitriles **108** at room temperature in chloroform (04JFC1853) (Scheme 36).
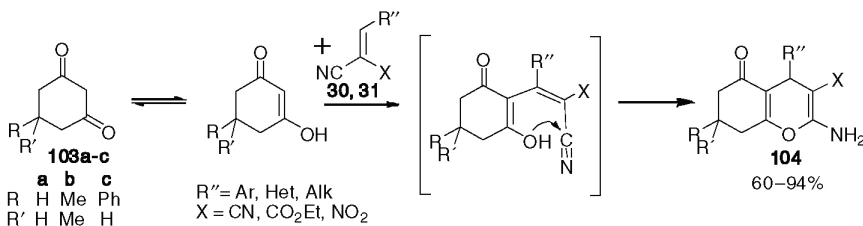
Scheme 34

Scheme 35
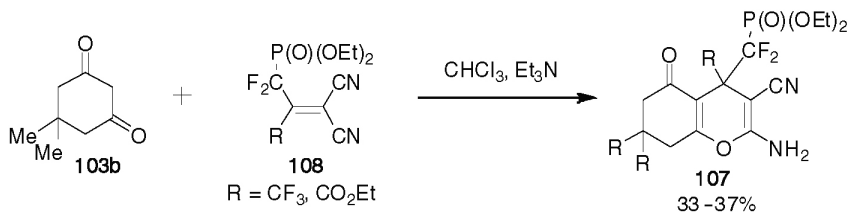
Scheme 36

Studies of the reactions of 2-phenyl-1,3-oxazinane **109** with nucleophiles revealed the possibility of obtaining pyrans **104** (96T14273). Probably, the reaction proceeds via an acid-catalyzed removal of the aminal protecting group. Simultaneous formation of a benzalcyanoacetic derivative or benzaldimedone, which undergoes subsequent heterocyclization, leads to **104** (Scheme 37). Thus, in this approach the 1,3-oxazinanes **109** can be considered as convenient masked aldehydes.

Recently, reactions of cyclic diketones **103** with UNs were carried out via solvent-free ball-milling of starting materials at 100–130°C (03T3753) or at room temperature in the presence of TEBAC (06SC2363) with nearly quantitative yields.

The three-component synthesis of tetrahydrochromenes **103** (Method 3) was found to be a very convenient approach (03RCB1164) (Scheme 38).

Subsequently, a large series of aliphatic aldehydes were employed using this method (04RJO567). That proceeds smoothly and facilitates the synthesis of a very broad spectrum of tetrahydrochromenes, which in turn has recently attracted many researchers from "green chemistry" in

Scheme 37

R = H, Me

Ar = 4Bu^{n}O-3-MeOC$_6$H$_3$, 5-Me-2-C$_4$H$_3$O, 4-ClC$_6$H$_4$, 2-C$_4$H$_3$S, 2,4-F$_2$C$_6$H$_3$, 2-O$_2$NC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 4-
O$_2$NC$_6$H$_4$, 4-C$_5$H$_4$N, 2,4,5-(MeO)$_3$C$_6$H$_2$, 4-Pr^{i}O-3-MeOC$_6$H$_3$, 3,4(—OCH$_2$O—)-2-ClC$_6$H$_2$, 4-
(H$_2$N(O)CCH$_2$O)C$_6$H$_4$, 4-(N-morpholinyl)C$_6$H$_4$,4((N-morpholinyl)CH$_2$CH$_2$O)$_3$OMeC$_6$H$_3$, 2-FC$_6$H$_4$, 4-MeOOCC$_6$H$_4$
X = CN, CO$_2$Me, CO$_2$Et, CO$_2$CH$_2$CH$_2$OMe, CO$_2$Pr^i, CO$_2$Bu^t, CO$_2$CH$_2$Ph
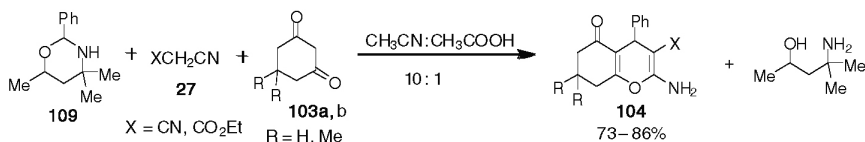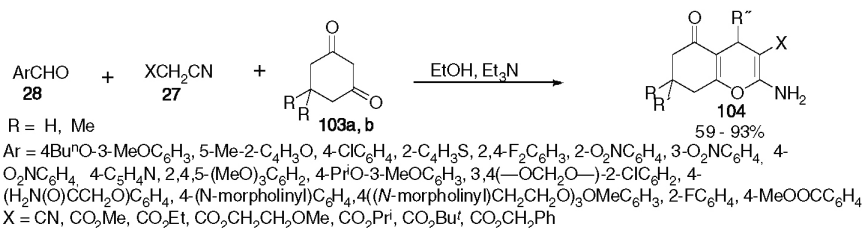
Scheme 38

attempts to make this procedure more eco-friendly. New conditions and catalysts for Method 3 have been suggested: LiBr, solvent free (06SL1928), NH$_4$H$_2$PO$_4$ in water or aqueous ethanol (07SC1097), hexadecyltrimethylammonium bromide (04SL871) or Bu$_4$N$^+$F$^-$ (**104**) in water, I$_2$ in DMSO (07SC4353), perfluorooctanoates of rare-earth metals La(C$_7$F$_{15}$COO)$_3$ and Yb(C$_7$F$_{15}$COO)$_3$ in ethanol (06JFC97), N-methylimidazole in alcohol, water, or at solvent-free grinding (08M129). A natural chiral organocatalyst – L-proline – was applied for an aminopyran synthesis in H$_2$O or H$_2$O–EtOH media (06S263), but unfortunately, the authors do not provide any data on the stereoselectivity. Tetrahydrochromenes **103** were synthesized in an ionic liquid (1,2,3,3-tetramethylguanidinium trifluoroacetate) (05CAL39), while microwave assistance was used to promote the reaction in a catalyst-free aqueous suspension (07SC3961), or in the presence of silica-grafted amine (06H(68)889). Electrocatalysis (n-PrOH–KBr, 0.03 Faradays/mol) was also applied (06EJO4335). Almost in all the cases authors managed to reach high or quantitative yields. However, sometimes utilization of complicated or expensive reagents (in comparison with a conventional procedure) made this an unreasonable approach.

Very interesting transformations were observed with dimedone **103b** and arylidenethioacetamides **110** (88ZOR460). When the reaction was carried out at ambient temperature, Michael adducts **111** were formed. Compounds **111** can be converted on heating into hydrogenated pyridinethiones **112** (in ethanol) or to 2-aminopyran-3-thioamides **113** (in benzene). The formation of the latter ones was found to be reversible. Thus, **113** convert into **112** on heating in ethanol, and yield 2-amino-3-cyanopyrans **104** when heated with MN in benzene (Scheme 39).

Subsequent studies on thioamide pyrans with application of the "competitive reactions" method contribute to our understanding of the mechanisms of heterocyclizations with cyanothioacetamide **114** (89ZOR1331). 2,6-Diaminothiopyrans **115**, on heating in benzene, open their thiopyran ring reversibly forming intermediate **116**, which can eliminate cyanothioacetamide **114** or malononitrile **27a** with formation of UNs **30** or **117**, respectively. The direction of the subsequent reaction with
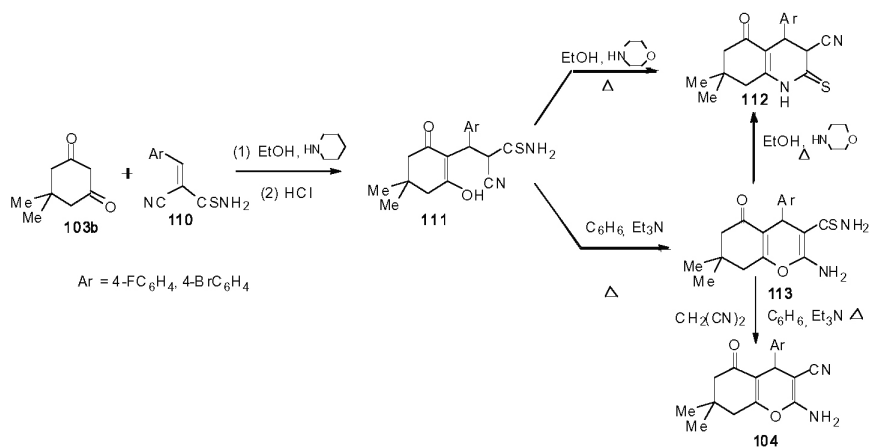
Scheme 39

ketones is determined by equilibrium **114** + **30** ⇌ **27a** + **117**. Reaction with dimedone affords 2-aminopyran **104**, but with monoketones, acetylacetone and acetoacetic ester give thiones **118** (Scheme 40).

Reactions of cyclic diketones with TCE **33** or diethyl dicyanofumarate **34** (74JCS(P1)2595, 70ZNB1423) result in the formation of 4,4-disubstituted tetrahydrochromenes **119**. 1,3-Indanedione **120** couples with **34** in absolute ethanol to afford the corresponding aminopyran (74JCS(P1)2595) (Scheme 41). But **120** with TCE gave only 2-dicyanomethyeneindandione-1,3, and the authors failed to isolate 4,4-dicyanopyran or the Michael adduct. These differences possibly can be attributed to the action of the four cyano groups, which destabilize the Michael adduct and promote its cleavage. Ester **34** reacts with dimedone **103b** easily, and both
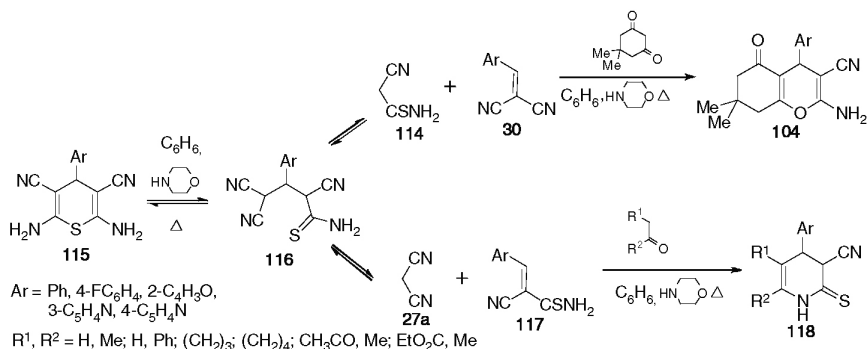
Scheme 40
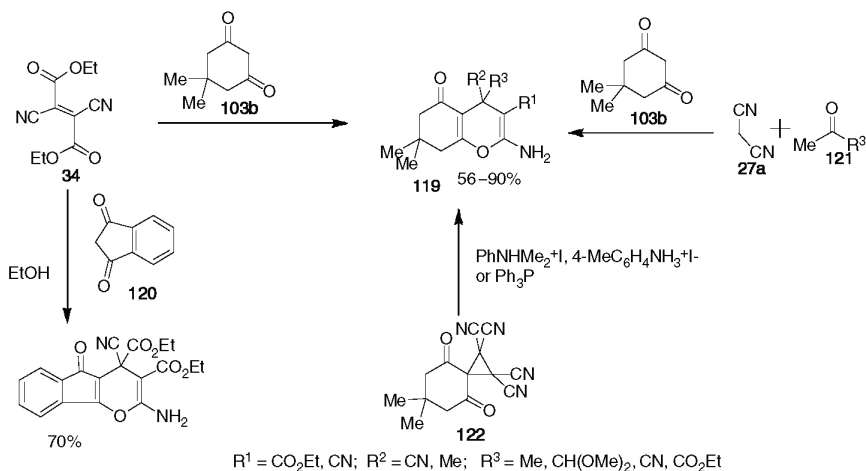
Scheme 41

pyran **119** ($R^1=R^2=CO_2Et$, $R^3=CN$) and cyclizable Michael adducts have been isolated (74JCS(P1)2595). Analogous pyrans were obtained via the reaction of MN, dimedone **103b**, and acetone or 1,1-dimethoxyacetone **121** (97JCS(P1)1323) or by cleavage of spirocyclic propane **122** by the hydroiodides of aromatic amines or triphenylphosphine (98CHE148, 98RJO1269) (Scheme 41).

The only known example of 2-monoalkylaminopyran **123** in the series of tetrahydrochromenes was obtained by the less common three-component reaction of alkylisonitriles **124**, acetylenedicarbonic esters **125**, and dimedone or 1,3-cyclohexanedione **103** (03M1585) (Scheme 42). This example illustrates how the isonitrile $-N^+\equiv C^-$ group can be involved in the formation of a 2-aminopyran ring, similar to the other groups with triple bonds – nitrile $C\equiv N$ and alkynyl $C\equiv C$.

Condensation of 1,3-dicarbonyl compounds with nitriles **27** does not always lead to aminopyran formation because the pathway depends on many factors. For example, 2-formyldimedone **126** with MN (82ZOR2361)
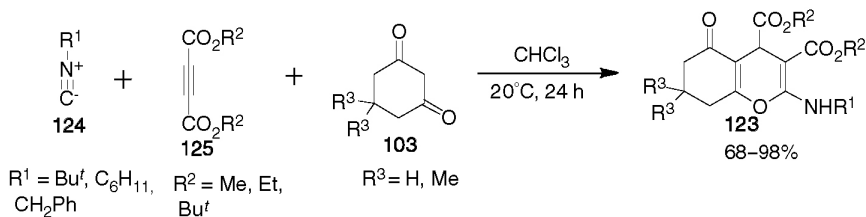
Scheme 42
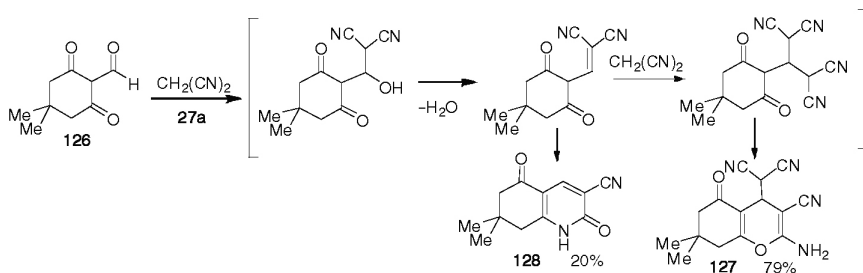
Scheme 43

leads to a mixture of 2-aminopyran **127** (79%) and hydrogenated quino-lone **128** (20%) (Scheme 43).

Method 2, which involves the reaction of unsaturated carbonyls with methylene-active nitriles, can be illustrated with pulegone **129** and MN **27a** (3 equiv.) in the presence of KF as a mild base (70CJC3064) (Scheme 44).

2,6-Diarylidenecyclohexanones **130** react in the presence of a base with 1 equiv. of nitrile **27** to give pyrans **10** (73AP463, 74AP367) (Scheme 45).

Recently, this method has been modified by application of a milder base (KF/Al$_2$O$_3$, alumina, coated with potassium fluoride) (04SC1425). *N,N*-Diethylpropin-1-amine **79** can be substituted for nitriles **27**, so *N,N*-disubstituted pyrans **131** can be obtained (73JHC165) (Scheme 46).

Scheme 44

Ar = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$
R = H, Bu^t
X = CN, CO$_2$Me
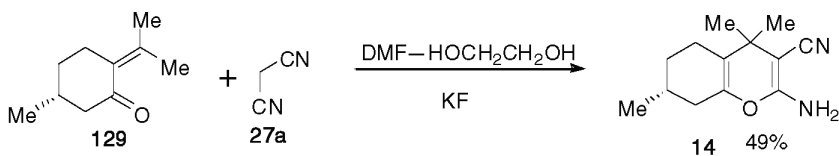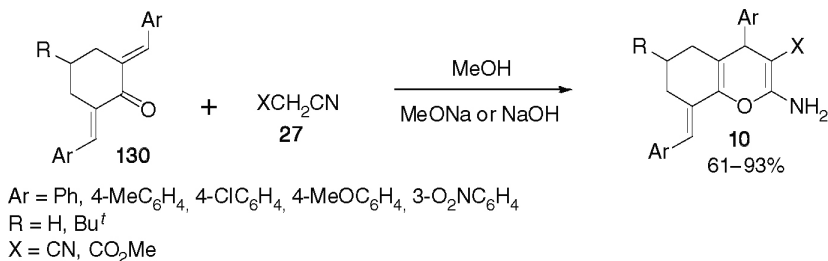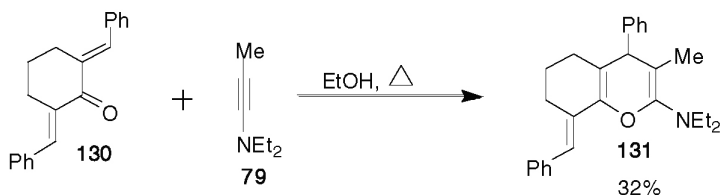
Scheme 45

Scheme 46

Moreover, unsaturated 3,5-diarylidenepiperidin-4-ones can be substituted for diarylidenecyclohexanones **130** (07BML6459). Analogously, a series of tertralones **132** were employed in the synthesis of tricyclic pyrans **133** (79M115) (Scheme 47).

A modern modification is carried out in DMF with KF/Al$_2$O$_3$, yields being close to quantitative (04SC3265). Arylidenetetralones **132** were treated with aminoacetylenes **134** (93JP13055). The authors attribute low yields of aminopyrans **135** (about 10%) to their decomposition on the chromatographic column with formation of 2-pyrones **136** (Scheme 48).

Similarly, **137** were synthesized from 2-arylidene-1,3-indanediones **138** (93JCS(P1)3055) in higher yields because the authors purified the products without chromatography (Scheme 49).

2-Aminopyrans, annulated directly with a seven-membered carbocycle, are very rare. One, **139**, is formed from substituted cyclohepta[c]furan-4-one **140** with UNs **30** (08CHE136) (Scheme 50).

Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$
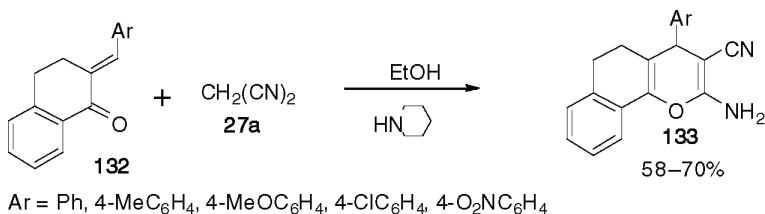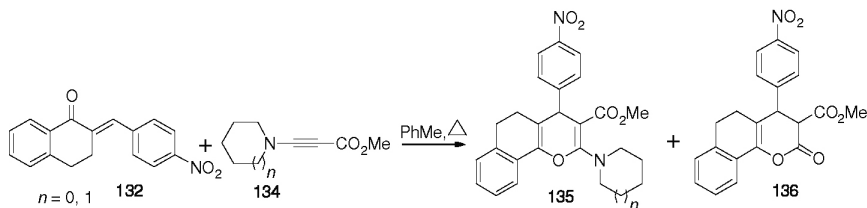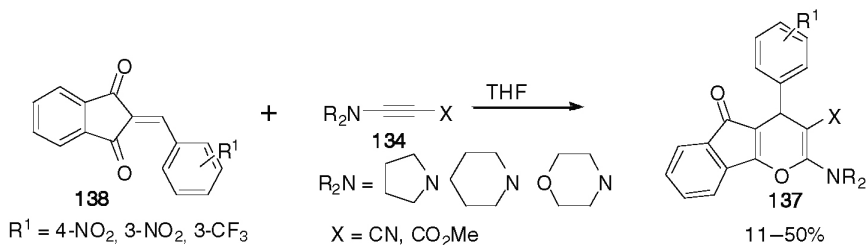
Scheme 47

Scheme 48

Scheme 49
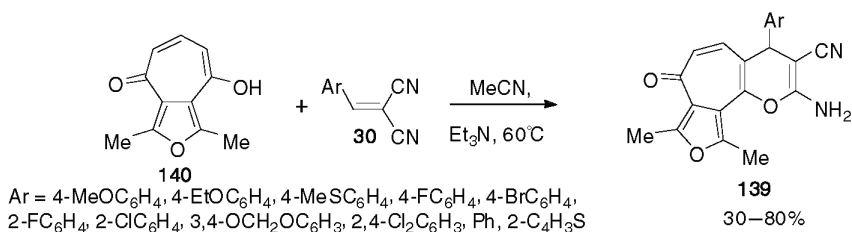
Scheme 50
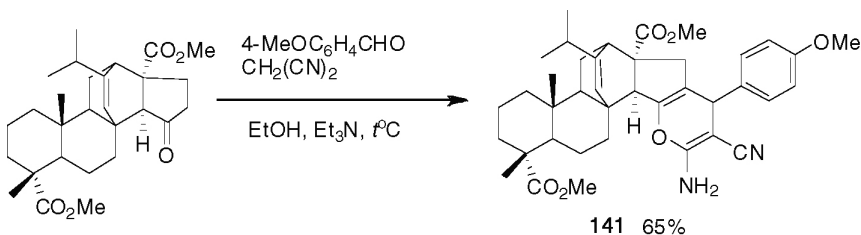
Scheme 51

An interesting example of a three-component aminopyran synthesis makes derivative **141** of cyclopentanopimaric acid (03RJO1738) (Scheme 51).

3.3 Synthesis of 2-amino-4H-benzopyrans (2-amino-4H-chromenes)

In the synthesis of 2-aminobenzo[b]pyrans **142** (2-aminochromenes) and condensed chromenes – naphthopyrans **143** and **144** and pyranoquinolines – diverse phenols **145** and naphthols **146** (77S871, 82ZOR2005, 83ZOR1782, 84S159, 87JOU369, 88CCC1534, 90IJB664, 90IJB885,

91BCJ668, 95BML2783, 96JHC27, 99H(51)2765, 00TL6993, 01FA965, 01T1395, 02RCB2238, 03SL2001, 04JME6299, 04MI2, 04MI3, 04SC509, 04TL2297, 05BML1587, 05BML4295, 05BML4745, 05TL3497, 06JHC1691, 06JME7731, 06RJO1813, 06TL7629, 07JME2858, 07T3093, 08BML603, 08JME417, 08JOC1954, 08SC1078, 08TL3276, 08TL7194), 8-hydroxyquino-line **147** (88CCC1534, 91BCJ668) or its sulfamino derivative (99H(51)2765), and 4-hydroxyindole (07JME2858, 08JME417) are used successfully (Scheme 52). Phenols and naphthols possess high C- and O-nucleophilicity and can be formally regarded as fully enolized carbonyl compounds. Resorcinol, *meta*-aminophenols, 1-naphthol, and 8-hydroxy-quinoline form the derivatives of 4*H*-chromenes both in the reaction with preliminary prepared UNs, and in the three-component condensation. In the case of *meta*-substituted phenols, the addition of UN **30** proceeds to position 6 (products **142**), rather than to 2, which has been erroneously considered in (90IJB664) (Scheme 52).

In the reaction of 1-naphthol with 3-nitro-4-fluorobenzalmalononitrile in ethanol, catalyzed by secondary amines, nucleophilic displacement of fluorine competes with pyran ring closure. Application of a tertiary amine (*N*-methylmorpholine) leads to the selective formation of the correspond-ing aminochromene (94H(38)399). 2,3-, 1,8-Dihydrooxynaphthalenes **148** and **149** react with 1 or 2 equiv. of aromatic aldehyde **28** and MN **27a** to yield naphthopyrans **150** and **151** or "dipyrans" **152** and **153** (90IJB885, 02RCB2238) (Scheme 53).

2,7-Dihydroxynaphthalenes **154** react only with 1 equiv. of an aromatic aldehyde and MN, possibly, due to steric constraints (02RCB2238) (Scheme 54).
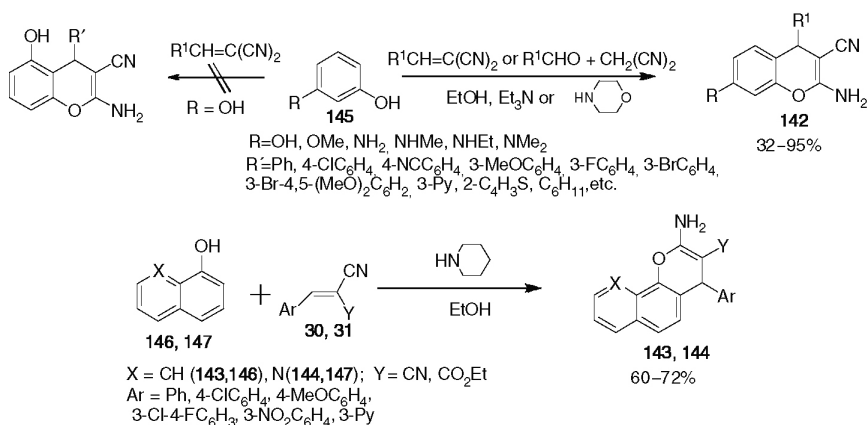
Scheme 52
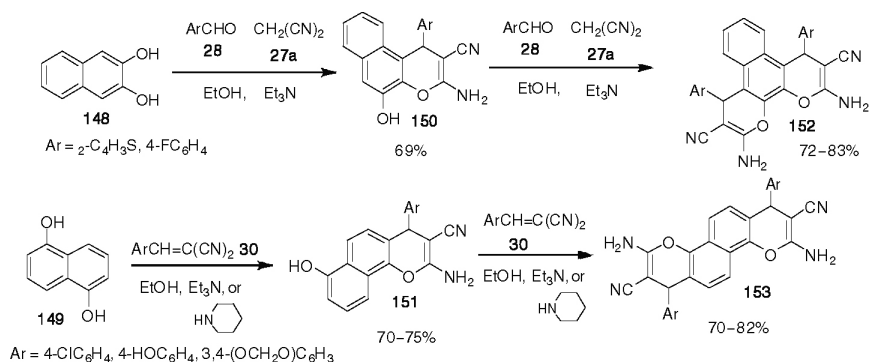
Scheme 53
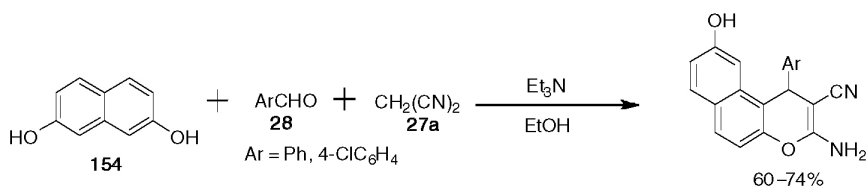
Scheme 54

Recently, 2-amino-4*H*-chromenes revealed a high antitumor activity *in vitro* (04JME6299). Subsequently, extensive SAR prompted the synthesis of various types of condensed aminochromenes (including representatives of new classes of fused heterocycles) (05BML4745, 07JME2858, 08BML603, 08JME417) (Scheme 55).
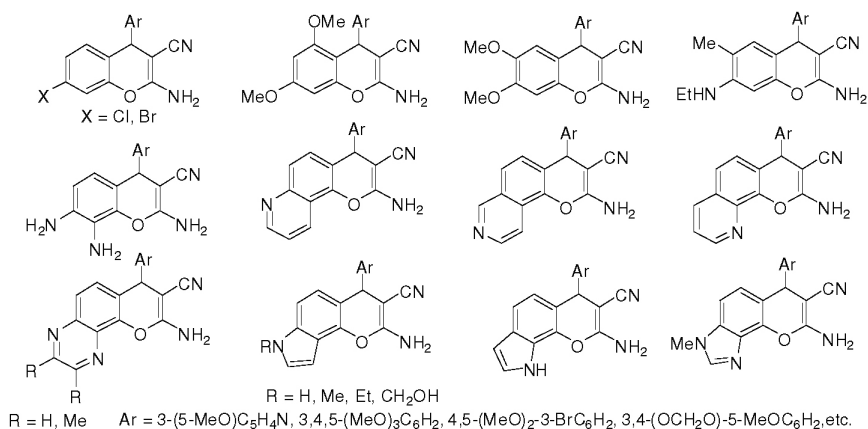
Scheme 55
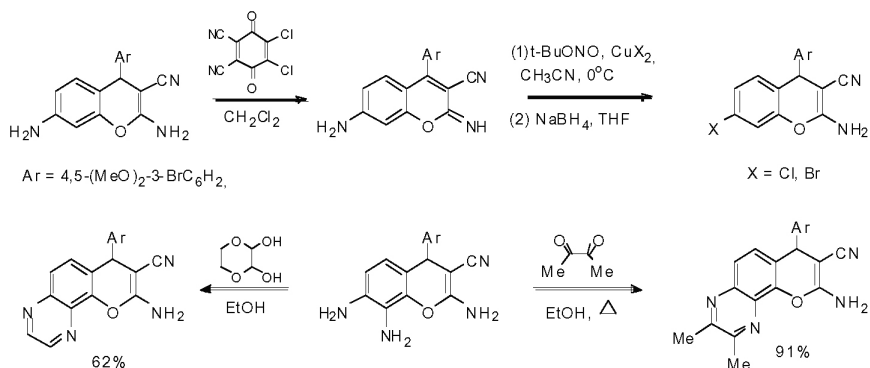
Scheme 56

As a rule, these compounds were obtained using phenols, hydroxy-quinolines, and other hydroxy-substituted heterocycles with UNs. In some cases aminochromenes were subjected to postsynthetic modifications (05BML4745, 07JME417) (Scheme 56).

The only known example of asymmetric reactions in the chromene series consists in the synthesis of **155** with asymmetric induction by nitriles **156** with a chiral menthyl substituent. Compounds **155** are formed in high yields, but with low diastereomeric purity, the major stereoisomer possessing the *S*-configuration (96JHC27) (Scheme 57).

Recent interest toward aminochromene synthesis is connected with attempts to design some new "green" synthetic procedures. As a rule, these syntheses are conducted by three-component method from the corresponding aldehydes, nitriles, and phenols. Aminochromenes have been obtained on refluxing in aqueous media in the presence of the quaternary ammonium salts trimethylcetylammonium chloride (01T1395) and
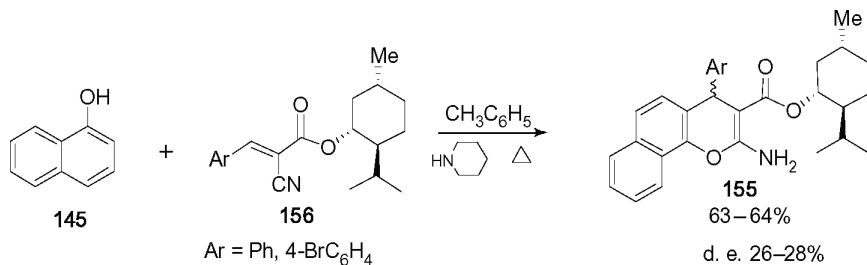
Scheme 57

tributylammonium bromide (03SL2001), as well as in ethanol with KF/ Al$_2$O$_3$ (04SC509), in water with γ-Al$_2$O$_3$ (04TL2297), and in EtOH with 0.3 equiv. of diazabicyclo(2.2.2)octane (08SC1078). There is a report on a three-component electrocatalytic synthesis of aminochromenes (solvents – EtOH, ^{n}PrOH, electrolite – KBr) (08TL7194). Solvent-free three-component syntheses were carried out in the presence of Zr(KPO$_4$)$_2$ (05TL3497) or TiCl$_4$ (06JHC1691, 06RJO1813). In the latter case purification requires extraction and preparative chromatography (eluent ethyl acetate–hexanes), which causes doubts about the benefit of this method as eco-friendly. Nanosized catalyst MgO facilitated the preparation of 2-amino-4*H*-naphtho[1,2-*b*]pyrans in water or aqueous ethylene glycol (07T3093). A microwave-assisted three-component synthesis in the H$_2$O–K$_2$CO$_3$ (05BML4295) requires ethanol for crystallization. Another example of the "green chemistry" of aminopyrans is illustrated by a three-component reaction in aqueous media using cetyltrimethylammonium bromide (0.1 equiv.) with ultrasonic sonification (04MI3). Both factors (interphase catalyst and sonification) are essential probably to stabilize the emulsion, which facilitates the interaction of the starting compounds. This "green" procedure possesses serious limitations: aldehydes with donor substituents do not react; 1-, 2-naphthols can be applied, but not resorcinol. Moreover, copious amounts of organic solvents, which are required for laborous isolation of the products, make this method complicated and noneco-friendly.

Somewhat different type 2-amino-4*H*-chromene synthesis is represented by the interaction of CH-acidic nitriles **27** with salicylic aldehyde **157** where the phenolic OH and aldehyde groups are present in the same molecule. A conventional mechanistic scheme is represented (Scheme 58), where in the presence of a base nitrile **27** condenses with the aldehyde to give Knoevenagel intermediate **158**. Then nucleophilic addition of the OH group leads to iminochromene **159**, which then adds a nucleophile (as a rule, the second equivalent of nitrile **27**) at position 4 to form 2-amino-4*H*-chromene **160**.

Isolation of intermediates **158** and **159** is complicated even when the reaction has only 1 equiv. of nitrile **27**. The last stage may be the fastest (84S159). Alumina (Al$_2$O$_3$) can serve as a catalyst and 2-hydroxy-1-naphthaldehyde can be substituted for salicylic aldehyde to afford corresponding naphtha[2,1-*b*]pyrans (08TL3276). Recently, biologically active **161a**, having received code HA14-1, has been found among this class. It is
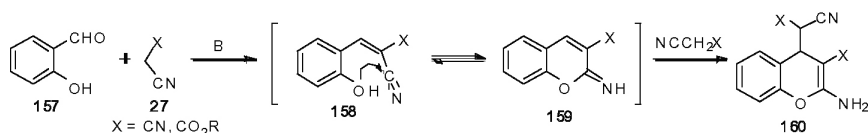
Scheme 58

able to inactivate antiapoptotic protein Bcl-2, and, consequently, prevent tumor growth.

161a   HA14-1
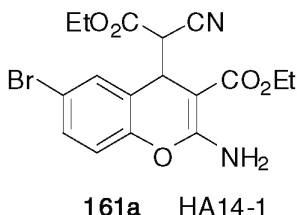
This inspired the publication of a series of papers devoted to the development of procedures for the synthesis of **161a** (00TL6993, 05TL3497, 06TL7629) and SAR-studies (05BML1587, 06JME7731). Molecular sieves (08TL3276), $Zr(KPO_4)_2$ (05TL3497) were applied as the catalyst, as well as electrocatalysis with NaBr–EtOH (06TL7629). Typical yields are about 50–90%. A new powerful methodology, which involves the isolation of protected intermediate **162** by using an aldehyde **163** with a "blocked" OH group, has been designed (08TL3276). Deprotection followed by nucleophilic addition of various CH-acids affords chromenes **164** with different substituents at C4 (Scheme 59).

However, all the broad spectrum of products formed via the reaction of salicylic aldehydes with methylene-active nitriles cannot be shown on a one simple scheme. In the presence of ammonium acetate different chromenes **165** and **166** can be isolated, depending on the order of addition of reagents, the amount of catalyst, and temperature (77S871) (Scheme 60).

Recently extensive mechanistic studies of this reaction involving kinetic ^{1}H NMR were conducted (08JOC1954). Thorough selection of solvents (water, MeOH, CH_2Cl_2, DMSO), catalysts (Et_3N, $NaHCO_3$, Na_2CO_3), and conditions allowed selective isolation of iminochromenes **159**, 4-dicyanomethylenechromenes **160**, as well as bis-chromenes **167** and **168**, and to study their mutual conversions (Scheme 61).

Unusual polycyclic **169** was obtained from salicylic aldehyde **157** and cyanoacetylated bisindole derivative **170** (07JOC5886) (Scheme 62).

Scheme 59

Scheme 60

R = H, 8-OMe, 8-OH, 6-Br, 7-NEt$_2$, 7,8-(OH)$_2$, 8-OMe+6-Br

Scheme 61

169   72%
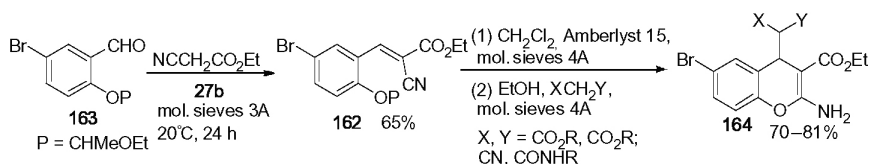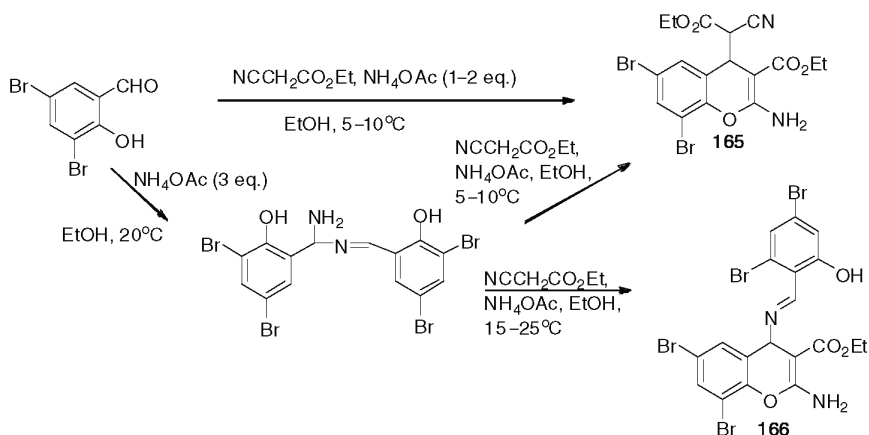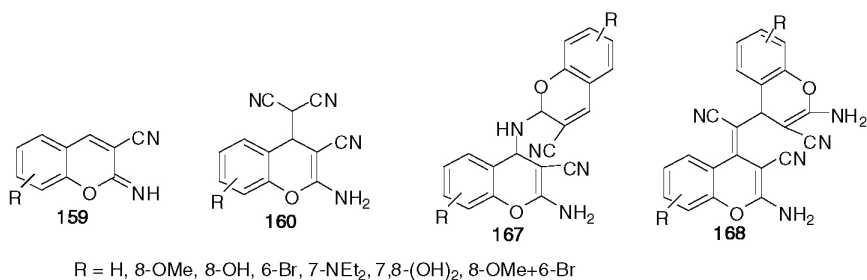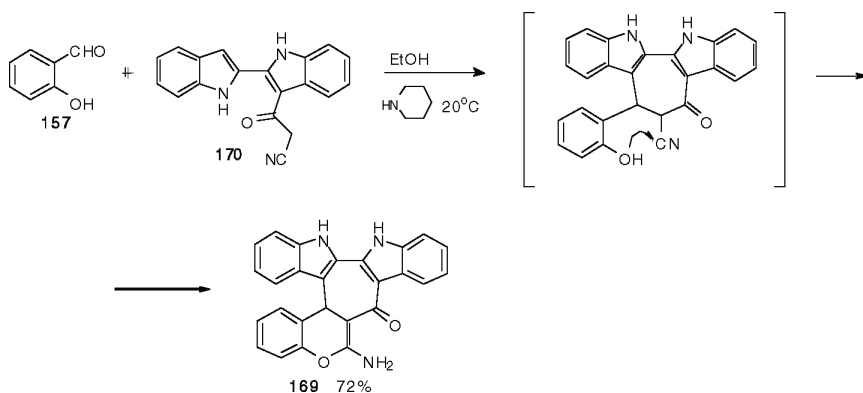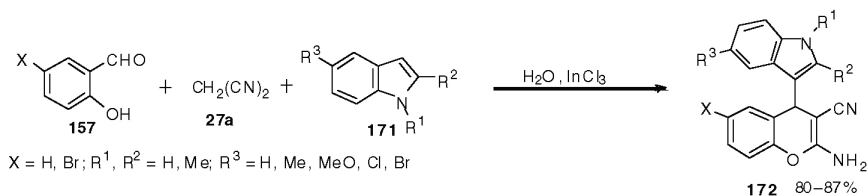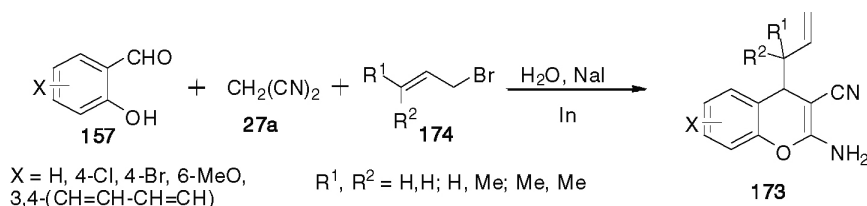
Scheme 62
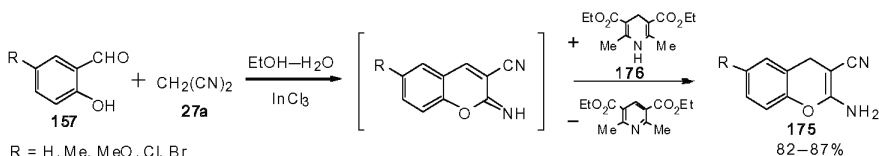
Scheme 63

Scheme 64

Scheme 65

Addition of indoles **171** to a mixture of salycylic aldehyde **157** and malononitrile **27a** affords 4-(3-indolyl)-substituted 2-amino-4*H*-chromenes **172** (07TL6785), probably the result of an addition of indole to intermediate iminochromene **159** (Scheme 63).

Alkylation products **173** of iminochromenes **159** were synthesized using allyl bromides **174**, NaI, and metallic indium. The indium-meditated reaction is accompanied by a complete allyl rearrangement (08SL2791) (Scheme 64).

Finally, 4-unsubstituted aminochromenes **175** were made in the presence of Hantzsch's 1,4-dyhydropyridine **176** by reduction of the intermediate iminochromene (07TL6785) (Scheme 65).

3.4 Synthesis of heteroannulated 2-amino-4*H*-pyrans

Heterocyclic methylene-active carbonyl compounds (or their tautomers) with arylidenemalononitriles yield 2-amino-4*H*-pyrans condensed with
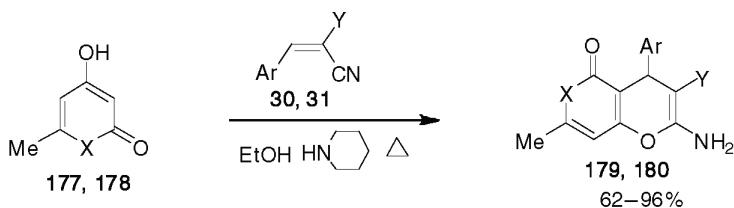
X = NH, NAlk (**177, 179**), O (**178, 180**); Y = CN, CO$_2$Et; Ar = Ph, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-Cl-6-FC$_6$H$_3$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$

Scheme 66

heterocycles. 4-Hydroxy-6-methylpyridones **177** (97BCJ1625, 00MOL19) and triacetic acid lactone **178** (98RJO552, 00MOL19, 04RCB573, 07BML3872, 08JME2561) afford pyranopyridones **179** and pyranopyranones **180** (Scheme 66).

Reaction proceeds with high yields of the pyrans only in the absence of strongly donating groups in the aryl fragments (e.g., dimethylamino group), which deactivate unsaturated nitrile (98RJO552). For compounds **179** and **180**, the three-component reaction also was successful and was extended to aliphatic aldehydes, while utilization of an ionic liquid [(bmim)(PF$_6$), 1-butyl-3-methylimidazolium hexafluorophosphate] instead of ethanol increased the yields of pyrans by 10–15% (04RCB573). Application of 1,1,3,3-tetramethylguanidinium trifluoroacetate as the solvent does not provide significant advantages (05CAL39).

Kojic acid **181** (97TL5301, 04RCB724) forms pyranopyranones **182** with UNs **30** and **31** (Scheme 67).

4-Hydroxyquinolone **183** (88CCC1534, 91BCJ668, 08JME2561) and 4-hydroxycoumarin **184** react similarly (Scheme 68).

The synthesis of **186** with a 3-thioamide substituent (93ZOR1465) succeeded. Several pyrano[3,2-*c*]coumarins **186** and their derivatives possessing promising antibacterial and fungicidal activity were also synthesized (01MOL519, 03MOL275).

X = CN, CO$_2$Et
Ar = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-CF$_3$SC$_6$H$_4$
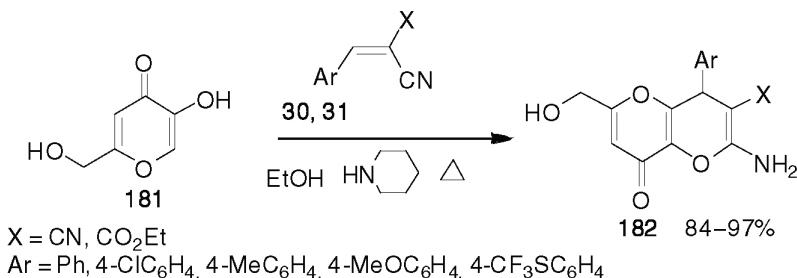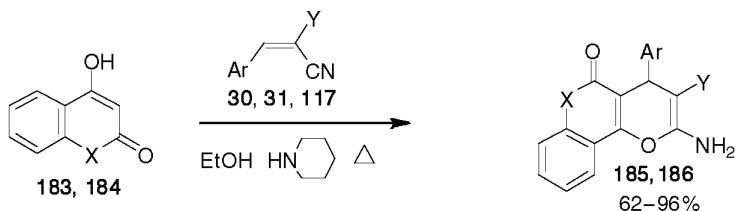
Scheme 67

X = NMe (**183, 185**), O (**184, 186**); Y= CN (**30**), CO₂Et (**31**), CSNH₂ (**117**);
Ar = Ph, 2-ClC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 2-Cl-6-FC₆H₃, 4-MeC₆H₄, 4-MeOC₆H₄,
4-NO₂C₆H₄, 3-NO₂C₆H₄

Scheme 68

Heterocyclizations with fused pyridone **187** opens access to a series of polyannulated pyrans **188** (03RCB2185, 06S2357) (Scheme 69).

The only known aminopyrans **189**, fused with a six-membered sulfur-containing heterocycle, were obtained from thiochromenone **190** with arylidenemalononitriles **30** (91EJM221) (Scheme 70).

Reactions of barbituric and *N,N*-dimethylbarbituric acids **191** with UNs **30** and **33** open access to pyrano[2,3-*d*]pyrimidinones **192** (73CB914, 84JOU2236, 03TL8307, 05CAL39) (Scheme 71).

The structure of the products and mechanistic considerations are proved by independent synthesis from 5-benzalbarbituric acid
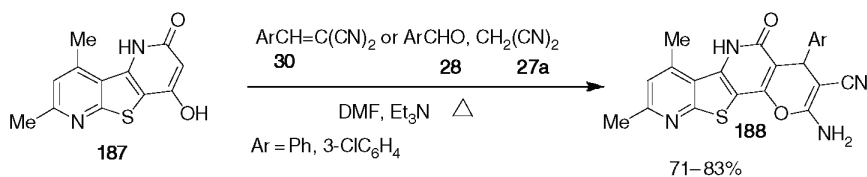
Scheme 69
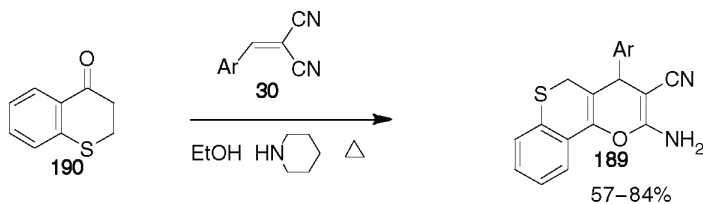
Ar = Ph, 2-ClC₆H₄, 4-ClC₆H₄, 4-MeOC₆H₄, etc.

Scheme 70

$R^1 = H, Me$
$R^2, R^3 = CN,CN; H, Ar$
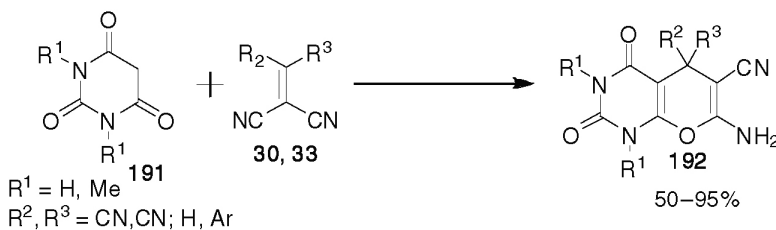
Scheme 71

(84JOU2236). In the case of TCE **33** the cyclization proceeds without a catalyst on short heating (73CB914). However, continuous heating leads to bis(6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)malononitrile. Modern modification involves a three-component reaction of aromatic aldehyde, malononitrile, and barbituric acid with solvent-free conditions under microwave irradiation (4–8 min, 70–95%) (03TL8307).

6-Amino-2,4-dihydropyrano[2,3-]pyrazoles **193** have been studied the most extensively among 2-aminopyrans condensed with five-membered heterocycles. The first heterocyclization of 3H-pyrazol-3-ones **194** into pyranopyrazoles **193** used TCE **33** (73CB914). Subsequently, N-phenyl substituted **194a** (80KG1420) and NH-pyranopyrazole **194b** (83JOU150) were used in Method 1. Similar pyrans were obtained from 4-arylidenepyrazolons **195** and MN **27a** (80JPR831, 83JOU2291, 86AKZ608) (Method 2). Papers (83JOU2291, 02CHE1180, 09TL2252) suggest a convenient three--component synthesis of pyranopyrazoles **193** from aldehydes, MN **27a** and pyrazolones **194** in the presence of organic bases (Method 3) (Scheme 72).

Mechanistic considerations, which involve the formation of a Michael intermediate **196**, have been reported (83JOU2291). Reaction of UNs **30** with pyrazolones **194** on heating in methanol with catalytic amounts of morpholine leads to pyranopyrazoles **193** in high yields. Short interaction of the same reactants in the absence of a catalyst at room temperature gives substituted pyrazoles **196**, which can be cyclized into pyranopyrazoles **193** on heating with a base where **196** is the main intermediate. Its high reactivity was proven when authors (80JPR831, 83JOU2291) failed to isolate **196** in the reaction of arylidenepyrazoles **195** with MN **27a**, which proceeds only in the presence of a base to give pyranopyrazoles **193**.

Recently, a completely new four-component heterocyclization of pyranopyrazoles **193** has been designed (09RCB2362, 09JCO914) (Scheme 73). It consists in the simultaneous mixing of aldehydes **28**, MN **27b**, ketoesters **36**, and hydrazine hydrate. Domino-type heterocyclization proceeds very regioselectively, probably, via formation of a pyrazolone **194** and UN **30**in situ. The method is very facile and facilitates preparation of a broad variety of pyranopyrazoles **193**.

Scheme 72

Ar = Ph, 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-MeOC$_6$H$_4$; R = Me, Ph; X = Ph (**a**), H (**b**), etc.
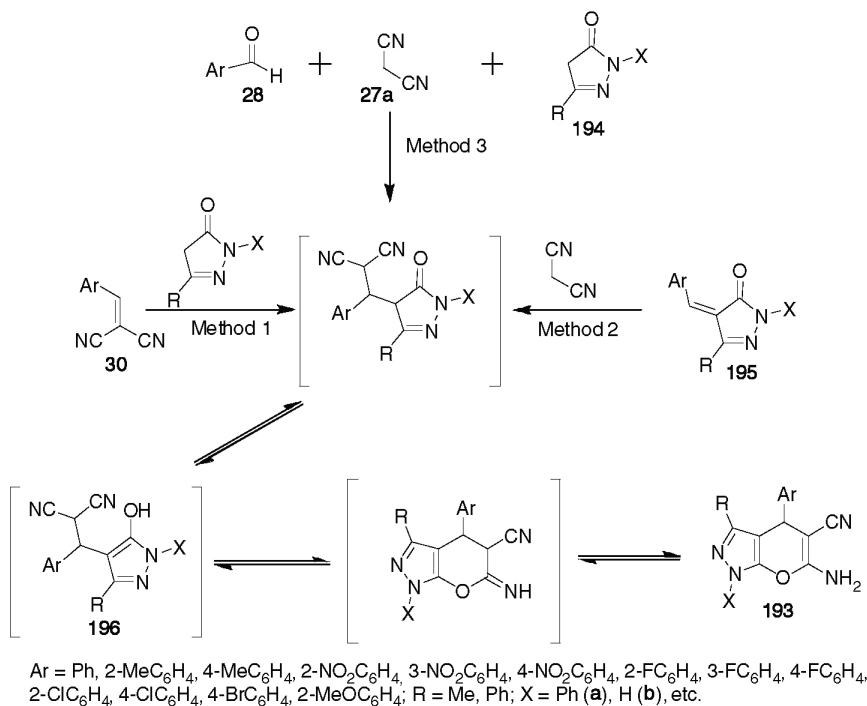
Methods 1 and 3 are versatile. Aliphatic aldehydes can be applied (99CHE1183, 05RJC952), as well as pyridylthiomethyl-substituted pyrazolones **197** and **198**, which give rise to pyridyl- **199** and 1,4-dihydropyridyl **200** substituted pyranopyrazoles (03RCB2207, 06S2357) (Scheme 74).

Scheme 73

Ar = Ph, 4-FC$_6$H$_4$, 2-O$_2$NC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$, 3-C$_5$H$_5$N, 2-C$_4$H$_3$S

Ar = 4-FC$_6$H$_4$
R^1, R^2 = OEt, 4-MeOOCC$_6$H$_4$; NHPh, 3-C$_5$H$_5$N
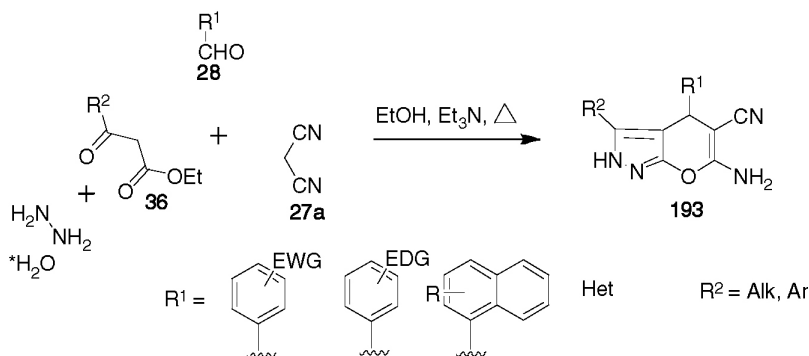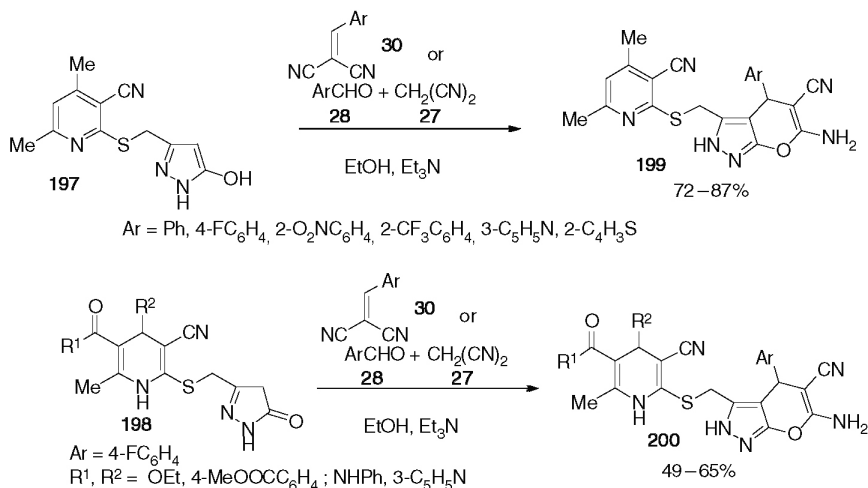
Scheme 74

Utilization of UNs with fluoroalkyl substituents **201** makes possible the synthesis of 4,4-disubstituted fluorine-containing pyrans **202** (02JFC63) (Scheme 75). Phospho- and fluoro-containing pyranopyrazoles **203** were obtained similarly (04JFC1853) (Scheme 75).

Recently, isocyanides were employed in the synthesis of *N*-monoalkyl pyranopyrazoles, difficult to obtain by other methods (08JCR222, 09T3492) (Scheme 76).

R^1 = H, Ph, 4-FC$_6$H$_4$, 4-F-2,6-Cl$_2$C$_6$H$_2$
R^2 = CHF$_2$, CF$_2$Cl, CF$_3$, CO$_2$Me
X = H, Cl

53−95%

R^1 = Ph, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$
R^2 = CF$_3$, CO$_2$Et

34−57%

Scheme 75

Scheme 76

Ar = Ph, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$, 2,3-Cl$_2$C$_6$H$_3$, 2-F-5-BrC$_6$H$_3$, 4-MeOOCC$_6$H$_4$, 3-C$_5$H$_4$N, 2-C$_4$H$_3$S
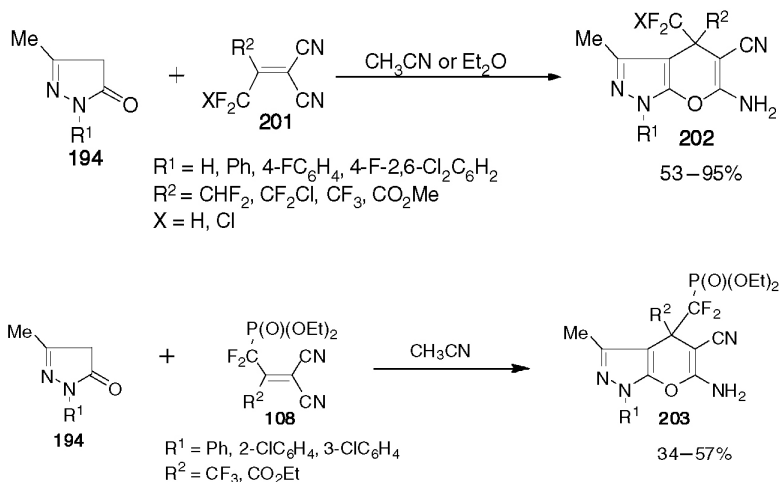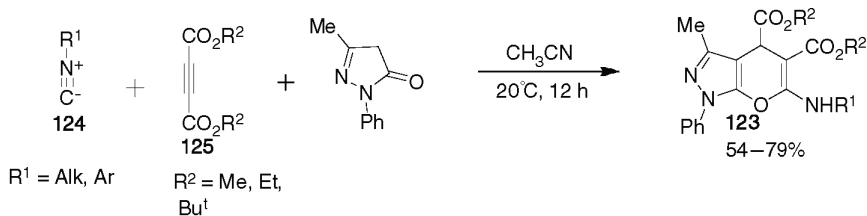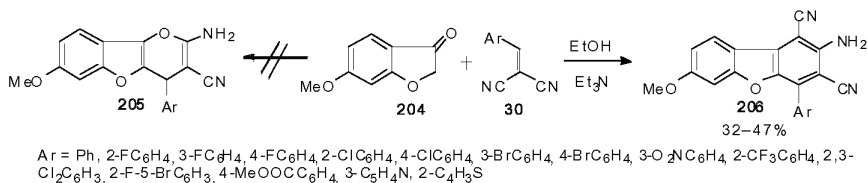
Scheme 77

Five-membered oxygen- and sulfur-containing heterocyclic ketones reveal notable reactivity (03RCB961, 03RCB1380). Benzo[*b*]furan-3-one **204** with arylidenemalononitriles **30** gives dibenzo[*b,d*]pyrans **206** instead of expected pyran **205** as a result of Michael reaction and the exchange of methylene components (03RCB961) (Scheme 77).

When benzo[*b*]thien-3-on **207** was substituted for benzo[*b*]furan-3-one **204**, aminopyrans **208** were obtained. Application of the three-component

Ar = Ph, 3-FC$_6$H$_4$, 4-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$, 4-MeOOCC$_6$H$_4$, 3-C$_5$H$_4$N, 2-C$_4$H$_3$S
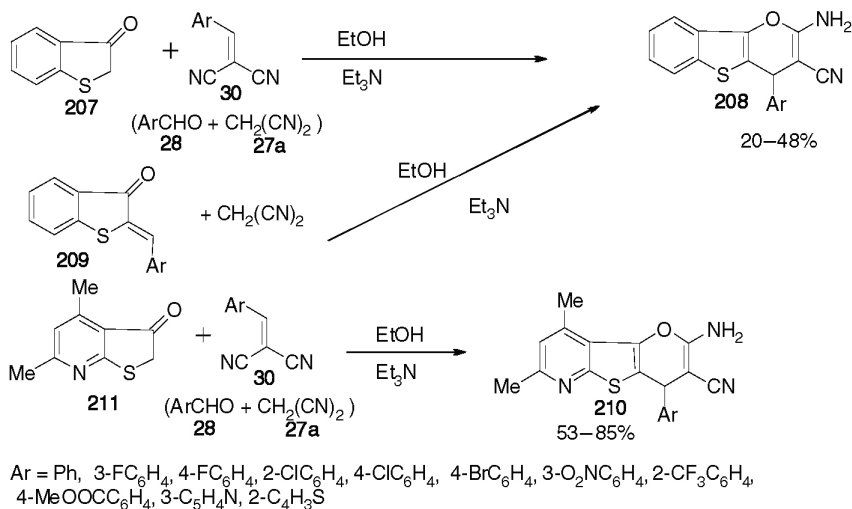
Scheme 78

modification is possible, as well as the utilization of presynthesized 2-aryli-denebenzo[*b*]thien-3-ones **209** (03RCB961). Thienopyrans **210** were obtained in the highest yields among the series, possibly, due to the relatively high methylene activity of thienopyridinone **211** (03RCB1380) (Scheme 78).

Similar pyrans, fused with indoles, have been obtained (85CHE191).

3.5 Synthesis of spiro-conjugated 2-amino-4*H*-pyrans

In contrast to acyclic monoketones, which usually do not form aminopyrans, reactions of cyclic ketones or their cyanomethylene derivatives with methylene-active carbonyl compounds give spiro-conjugated 2-amino-pyrans. Their syntheses are represented by fewer examples relatively to 4-arylpyrans, but many of the latter draw attention due to their promising biological activity. Most papers, concerning spiro-conjugated aminopyrans, are devoted to the synthesis of spiro(indole-3,4′-(4*H*)-pyrans) from isatine **212** and its derivatives. The first example of reaction of 3-cyanomethyleneindolone-2 **213** with 1,3-dicarbonylcompounds results in the formation of a series of spiro-annulated pyrans **214** (80CPB648) (Scheme 79).

tert-Butyl acetoacetete also reacts with 3-(dicyanomethylene)-2-indolone in the similar manner (89CB1323). Acetone and acetophenone (80CPB1540) undergo Michael addition toward **213**, but adducts **215** do not cyclize into pyrans due to their relatively low degree of enolization. On reduction of the latter adducts by sodium borohydride, the OH group thus formed immediately attacks the nitrile group with cyclization into 5,6-dihydropyrans (80CPB1540) (Scheme 80).

$R^1 = COMe, CO_2Et, COPh, H$
$R^2 = Me, Ph, CO_2Me$

$Z = CN, CO_2Et$

65–93%

Scheme 79

$R = Me, Ph$

41–98%

75–98%
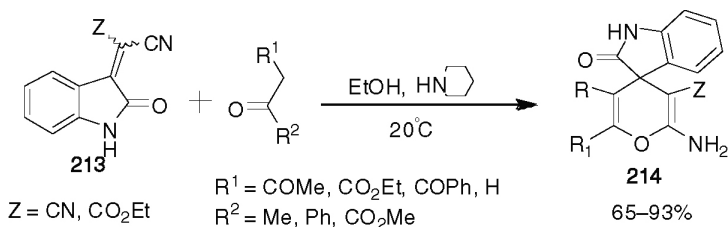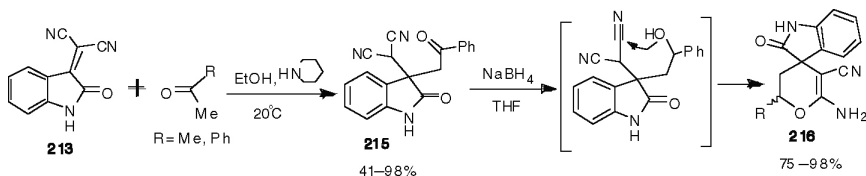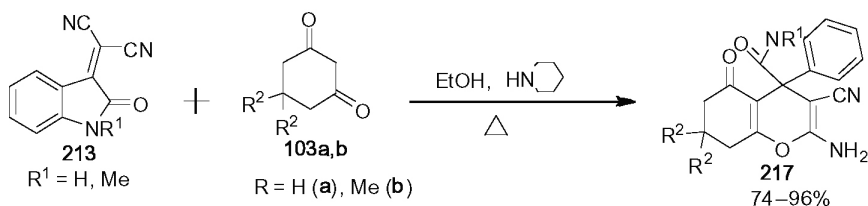
Scheme 80

Scheme 81

Application of 1,3-cyclohexanedione **103a** (80CPB648) and dimedone **103b** (89CB1323) gives the spiro derivatives of tatrahydrochromenes **217** (Scheme 81).

Subsequently, the syntheses of analogous compounds were carried out in three-component modifications in the presence of a base (08JCO741, 08RCB2373) or under electrocatalytic conditions (NaBr in MeOH, EtOH, ^{n}PrOH) (07T10543), as well as in water containing TEBAC (07T9365). Naphtho[2,1-*b*]pyrans result from the interaction of 3-(dicyano)methylene-2-indolone with β-naphthol (98OPP363), and naphtho[1,2-*b*]pyrans **218** and naphtho[2,1-*b*]pyrans **219**, spiro-conjugated with isatin moiety, were synthesized in solvent-free conditions containing InCl$_3$ (07T2057).
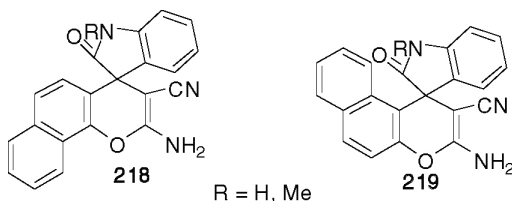
The base-catalyzed reaction of 4-hydroxycoumarin **184** with indolones **213** or with isatin and MN **27a** on short heating leads to spiro pyrano-benzopyrans **220** (89JHC1097, 05RCB992, 08JCO741, 08RCB2373) (Scheme 82).
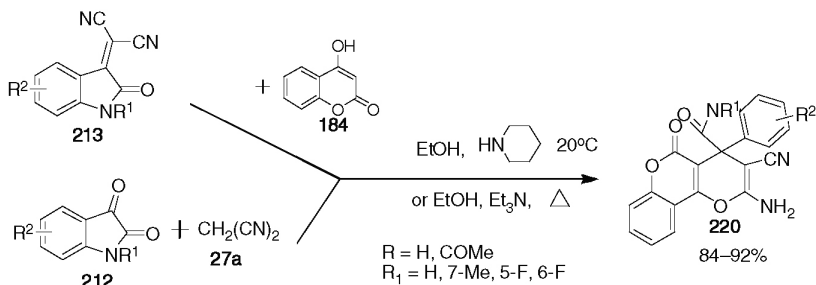
Scheme 82
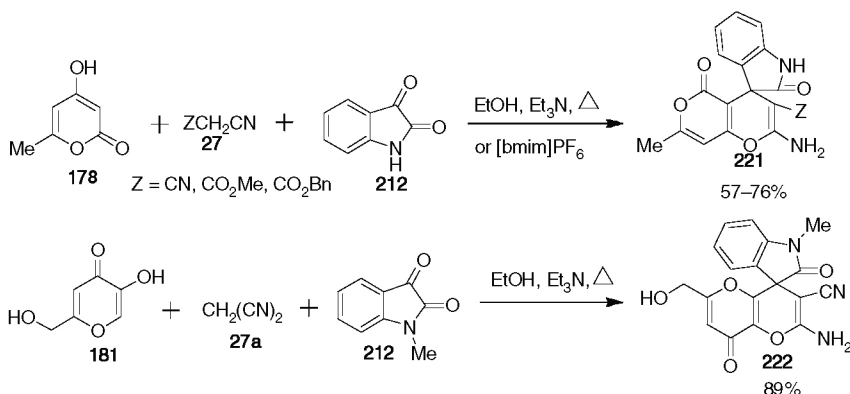
Scheme 83

A three-component reaction of lactone **178** with cyanoacetic deriva-tives in ethanol or ionic liquid (bmim)PF$_6$ proceeds smoothly with forma-tion of 2-aminopyrans **221** in high yields (04RCB724, 08JCO741, 08RCB2373), while kojic acid **181** acts in the same manner (04RCB724) (Scheme 83).

Under analogous conditions, the 3-cyanomethylene-2-indolones **213** react with barbituric acid and its derivatives **191** with the formation of spiro-annulated pyranopyrimidines **223** (88JIC202, 90H(31)31) (Scheme 84).

N-Methyl-4-hydroxy-2-quinolone **183** in a three-component reaction gives spiro pyrano[3,2-*c*]qionoline-2-ones (02MI2), but indolones **213** with 4-hydroxy-6-methyl-2-pyridone **177** react in a complicated way (97BCJ1625). Ethoxycarbonyl-methylene indolone (Z = COOEt) forms pyrans **224**, while dicyano analogs (Z = CN) yield substituted quinoline **225** (Scheme 85).

This unusual reactivity may be explained by nucleophilic addition of the 4-OH group of **177** to the 2-carbonyl of **213**, subsequent ring opening
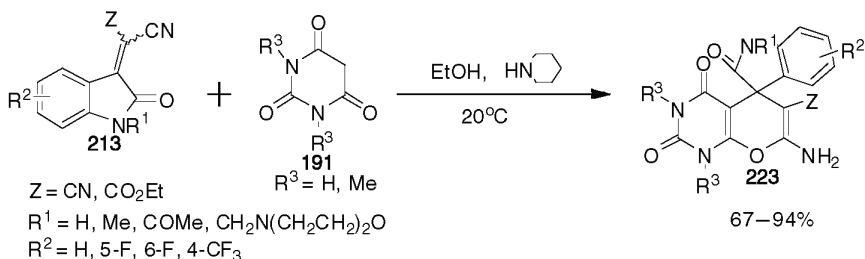
Scheme 84
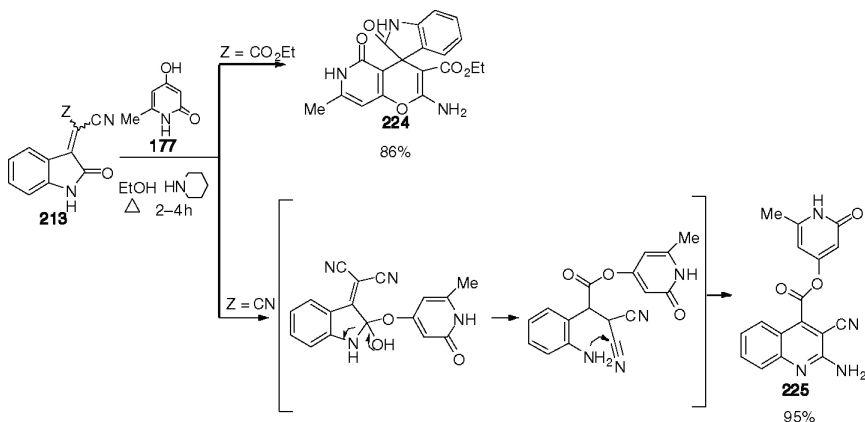
Scheme 85

and nucleophilic attack of the NH_2 group so formed on the nitrile group. This transformation is similar to the Pfitzinger reaction.

N-Phenylpyrazolone **194a** adds to indolones **213** to form spiro pyrano-pyrazoles **226**, which possess herbicidal activity (88JIC277) (Scheme 86).

A large series of spiro-annulated pyranopyrazoles were synthesized in base-catalyzed three-component reactions (08JCO741, 09JCO914).

1,3-Indandione **120** with indolones **213** forms pyrans **227** as the only products (89JHC1097, 08H(75)955) (Scheme 87).

R^1 = H, COCH$_3$, CH$_2$N(CH$_2$)$_5$, CH$_2$N(CH$_2$CH$_2$)$_2$O
R^2 = H, 5-F, 6-F, 4-CF$_3$
Z = CN, CO$_2$Et
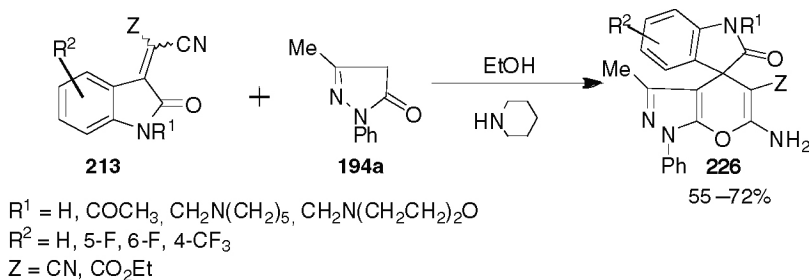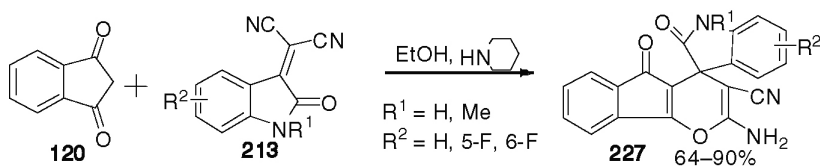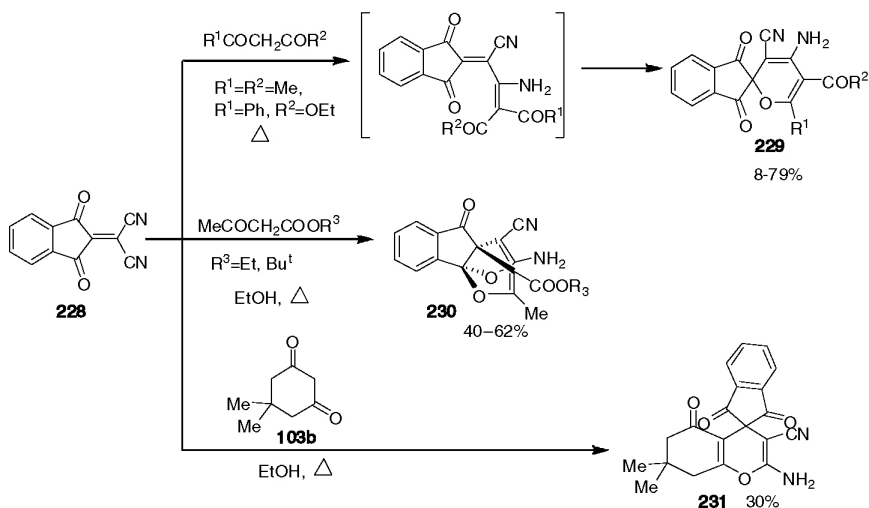
Scheme 86

Scheme 87

Scheme 88

The cyano derivative of indandione **228** acting as an unsaturated nitrile reacts differently with 1,3-dicarbonyl compounds, depending on their nature (89CB1323). Acetylacetone and ethyl benzoylacetate provide spiro(indan-2,2'-pyrans) **229**; acetoacetic esters give propellans **230** (proven by X-ray analysis). But only dimedone **103b** among the ketones studied yields spirochromene **231** (Scheme 88).

Acetylacetone derivatives of bis-dithiolobenzoquinone **232** show remarkable reactivity (95M615) with cyanoacetic acid derivatives **27** in ethanol with piperidine. They proceed via symmetrical elimination of two acetyl groups and subsequent cyclization to bis-pyrano derivatives **233** (Scheme 89).
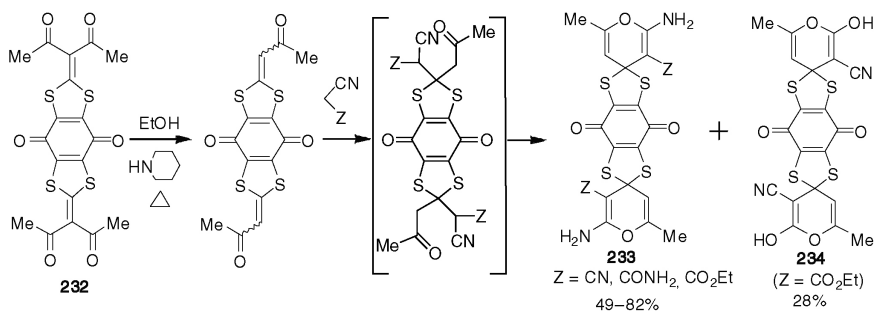
Scheme 89
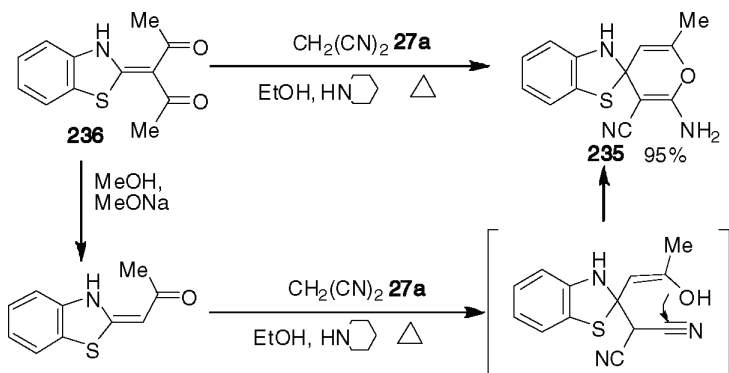
Scheme 90

Malononitrile and cyanoacetamide only give aminopyrans. However, in reaction with cyanoacetic ester **27b** aminopyran **233** has been isolated from the mother liquor and also side product **234** from the cooled mixture. Mechanistic considerations have been proved by the isolation of a deacetylated intermediate (95M615). Similar transformations occur in the synthesis of spiropyrans **235** from benzothiazole **236** (97G605) (Scheme 90).

Cyanoacetamide also forms 2-amino-3-carbamoylpyran, and cyanoacetic ester gives a mixture of 2-amino- and 2-hydroxypyran, with the prevalence of the latter.

Ketene dithioacetal **237**, obtained from acetylacetone, can serve as the initial reactant for the synthesis of aminopyran **238**, spiro-annulated with oxazolidine (00SC1269) (Scheme 91).

Knoevenagel adduct **239** of oxohomophthalimide **240** with malononitrile **27a** in reactions with CH-acids behaves ambiguously (82CPB1215). Reactions of **239** with acetylacetone, ethyl esters of acetoacetic and benzoylacetic acids, as well as methyl pyruvate led to the formation of the desired spiropyrans **241**. However, benzoylacetone, dibenzoylmethane, cyanacetamide, and oxindole always gave the same **242**. Authors explain this feature in terms of a retro-cleavage of adducts of Michael product **239**
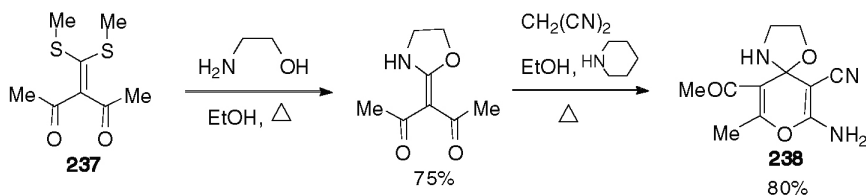
Scheme 91
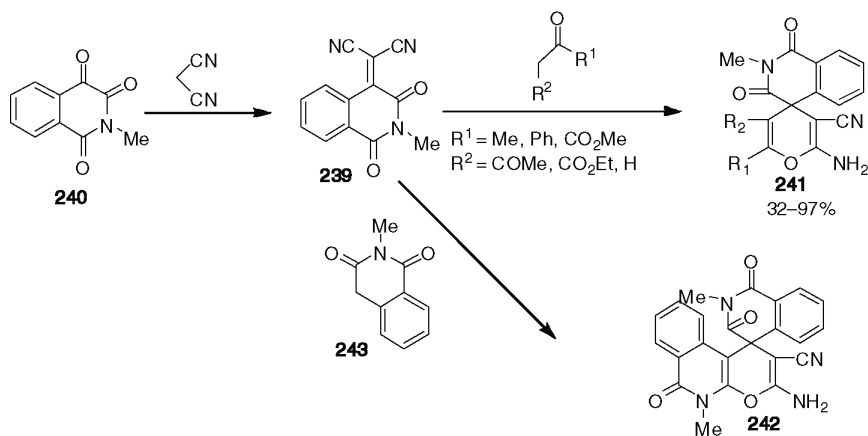
Scheme 92

with CH-acids to homophthalimide **243**, which thereafter reacts with **239** (82CPB1215) (Scheme 92).

Aminopyrans **244**, spiro-conjugated with an polycyclic N,O,S-system, have been synthesized using N,S-acetal derivatives of actylacetone and acetoacetic ester **245** (00PS(160)105). Diacetyl derivative **245** (Z = COMe) undergoes deacetylation in the course of pyran synthesis (Scheme 93).

A three-component reaction of piperidin-4-ones **246**, pyrazolones **194b**, and malononitrile **27a** represents a convenient approach to spiro **247** (02OL423) (Scheme 94).

N-Alkyl-substituted piperidines react autocatalytically at room temperature (in 82–84% yields). However, in the case of acceptor substituents R^1 (COMe, CO$_2$Et) a basic catalyst is required (triethylamine, yields 64–79%). In addition to Et$_3$N, an electrogenerated base from *n*-Bu$_4$NBr in CH$_3$CN was applied, enlarging yields by 12–15%. Charge consumption was 0.03–0.05 Faradays/mol, consistent with the catalytic mechanism. The other advantage of the three-component
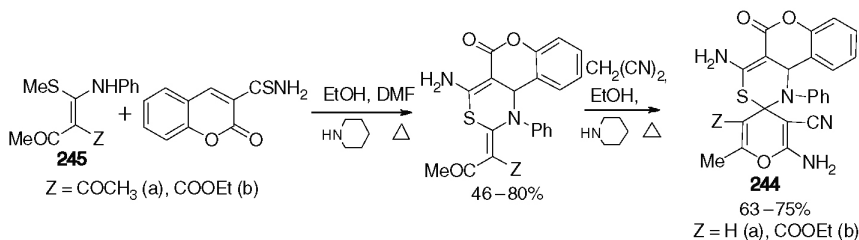
Scheme 93
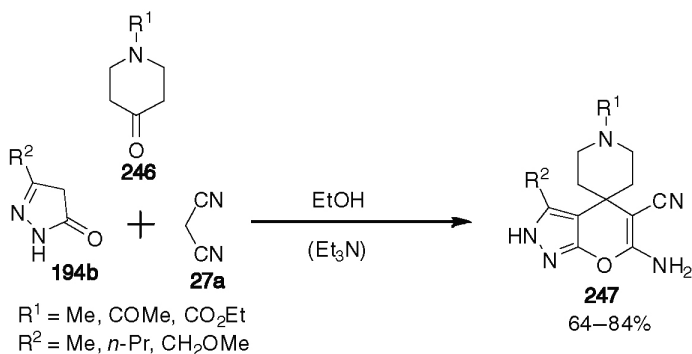
Scheme 94

reaction is avoidance of isolation of unsaturated piperidone–malononi-trile adducts, which are very unstable and tend to form dimers. Sterically hindered 1,2,5-trialkylpiperidones also form spiropyrans (03T7491). A possible mechanism has been proposed (03T7491)
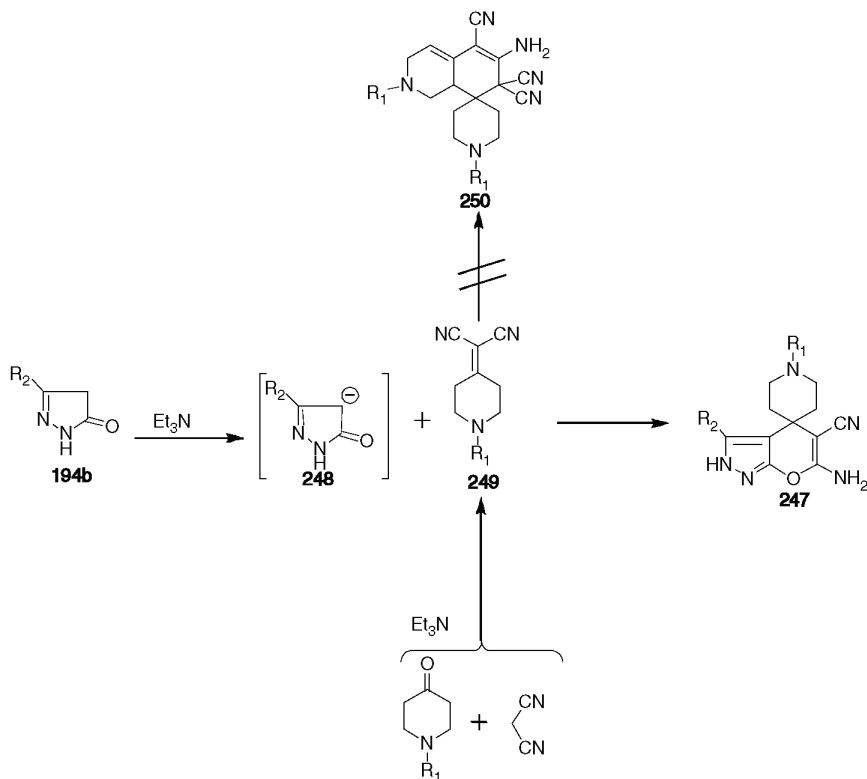
Scheme 95
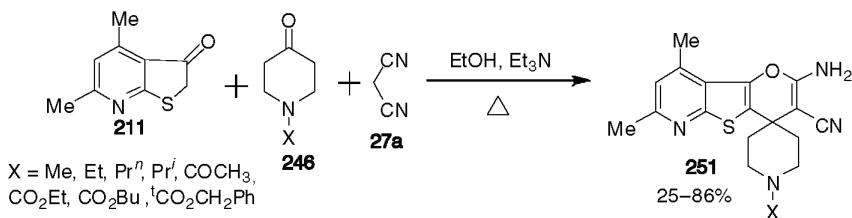
Scheme 96

involving a three-component "cross-reaction," in which intermediates **248** and **249** "meet at the reaction crossroads" and "continue their way" toward pyrano[2,3-c]pyrazoles **247**, rather than to hydrogenated quinolines **250** (Scheme 95).

A three-component reaction of thienopyridinone **211**, substituted piperidin-4-ones **246**, and malononitrile **27a** leads to spiro-conjugated polycycles **251** (03RCB1380) (Scheme 96).

Spiro cyclohexane-fused **252** were obtained in a similar reaction with 4-alkylcyclohexanes **253** and malononitrile **27a** (03RCB1380) (Scheme 97).

A new type of spiro-conjugated aminopyrans, pyrans, containing a cyclophane moiety **254**, were obtained from a carbonyl[2.2]paracyclophane derivative **255** in a two-step procedure with isolation of UN **256** (03T1739) (Scheme 98).
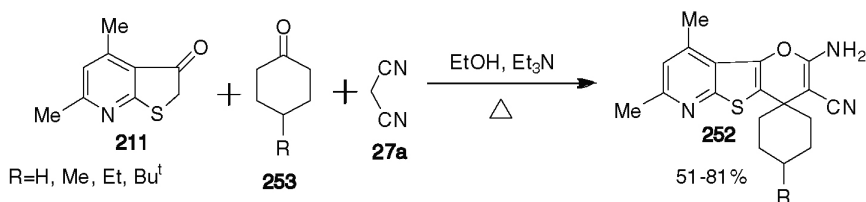
Scheme 97
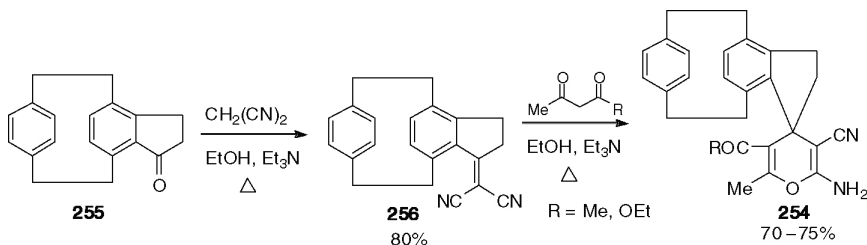
Scheme 98

4. CHEMICAL PROPERTIES OF 2-AMINO-4*H*-PYRANS

The reactivity of 2-amino-4*H*-pyrans as well as their chemical properties has been poorly studied because of their weak stability toward many reactants. They undergo ring opening and recyclizations in the presence of strong acids and bases, nucleophiles, and so on. But this feature can be turned to advantage in the synthesis of various heterocycles via recyclizations. Thus, the enamino moiety in 2-amino-4*H*-pyran-3-carbonitriles and 2-amino-4*H*-pyran-3-carboxylic esters provides access to diverse derivatives, including fused pyrans. The available data on the chemical properties of 2-aminopyrans are not systematic, and, in certain cases, are contradictory.

Photochemical contraction of pyran ring in 2-amino-4*H*-pyrans **255** leads to the formation of mixtures of cyclobutenes **256**, not easily accessible, accompanied with olefins **257** and alkynes **258** (89JOC3069, 97JCS(P1) 3401) (Scheme 99).

A mechanistic scheme involves intramolecular single-electron transfer (SET) from the enamino moiety toward carbon 5 of the ring, and subsequent transannular interaction in zwitter-ionic biradical **259** with formation of stabilized zwitter-ion **260**. Opening of the oxetane ring in **260** leads to cyclobutene **256**, while secondary photolysis of the latter gives olefin **257** and alkyne **258** (Scheme 100).

The presence of the enamino moiety in 2-amino-4*H*-pyrans accounts for their ability to undergo recyclizations into various pyridones, 1,4-dihydropyridines, and 2*H*-pyrones-2. To some extent, properties of 2-amino-4*H*-pyrans in reactions with nucleophiles can be compared to those of pyrillium salts (68T5059, 80T697) because they also tend to form recyclized products. Reactions proceed in the presence of bases or acids. Naphthopyrans **133** form 2-alkoxypyridines **261** on the action of sodium alcoholates or ethanolic NaOH (79M115) (Scheme 101).

R^1, R^2 = H, *i*-Pr; H, Ph, Me, Me; Me, Ph; (CH$_2$)$_4$, (CH$_2$)$_5$
R^3 = Me; Ph
G = CN; CO$_2$Et
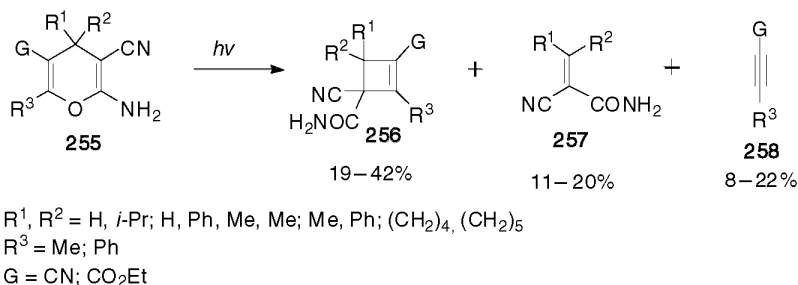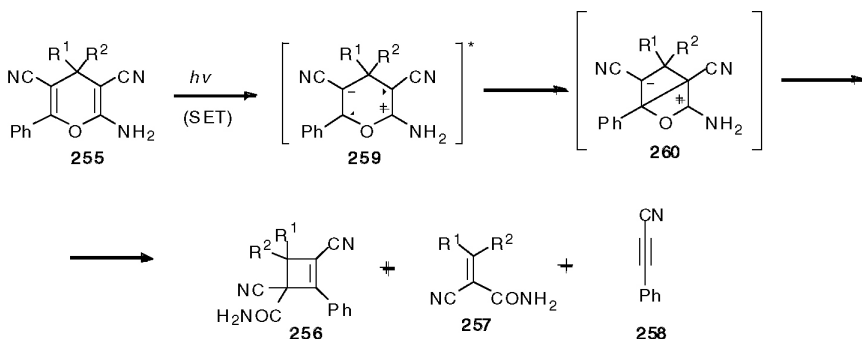
Scheme 99
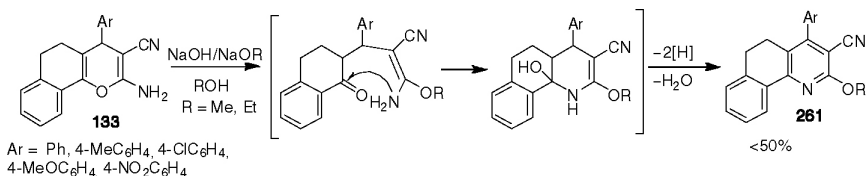
Scheme 100

Scheme 101

The reaction proceeds via ANRORC-recyclization induced by alkoxide ion, and subsequent oxidative aromatization. Authors believe that aromatization occurs at the expense of disproportionation of the intermediate dihydropyridine because yields never exceed 50%. These results were reproduced and expanded (00PHA269), and used in a synthesis of 4,6-diaryl-2-methoxy-3-cyanopyridines and annulated methoxypyridines (88TL2703) (with low yields).

Recyclizations in acidic media lead to diverse products depending on the conditions. Short-period action of concentrated sulfuric acid at 0°C (82ZOR2361) or 1 M HCl in DMSO at 50°C (95BML2783) affords coumarines or 3,4-dihydrobenzo[*h*]coumarines **262** (Scheme 102).
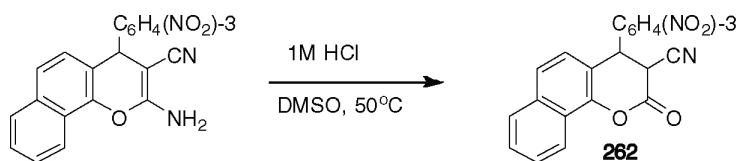
Scheme 102
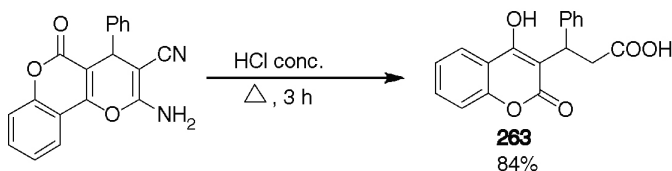
Scheme 103

On refluxing in 2 M (97JCS(P1)1323) or concentrated hydrochloric acid (62JOC3086), the following consecutive processes occur: hydrolysis of the enamine to the lactone, opening of the lactone ring, and hydrolysis of the nitrile to the carboxylic group followed by decarboxylation. Product **263** was utilized in the synthesis of blood anticoagulant and rodenticide warfarine (62JOC3086) (Scheme 103).

Utilization of acetic acid (90CCC718, 95BML2783) and mixtures of acetic and sulfuric acids (81JHC309), as well as triphenylmethylborofluoride (86JPR35), leads to 3-cyano-3,4-dihydropyridin-2-ones, which can be oxidized into the corresponding cyanopyridones by nitrosylsulfuric acid. Authors (81JHC309) have studied the synthesis of 3-cyanopyridones **264** systematically, and have shown that the latter can be obtained by different routes from 2-amino-4H-pyrans **59**, as well as from related dihydro- **265** and tetrahydropyridone **266** (Scheme 104).

Pyrans **59** with ammonium acetate in acetic acid generally lead to 2-aminopyridines **267** (81JHC309) in 40–50% yields, probably, due to disproportionative aromatization (Scheme 105).

Tetrahydrobenzochromenes **104** do not disproportionate under analogous conditions, giving hexahydroquinolines (89JPR971). Nonannulated pyrans, bearing a CN group in position 5, react in a more complicated manner (81JHC309) (Scheme 106). The strong electron-withdrawing action
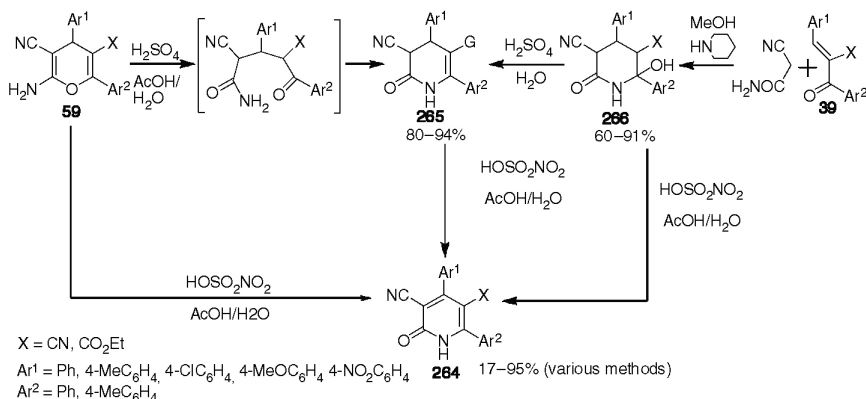
Scheme 104
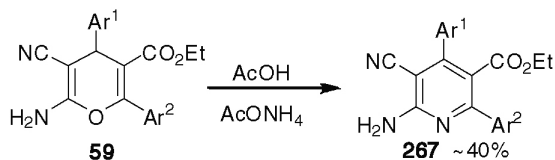
Scheme 105
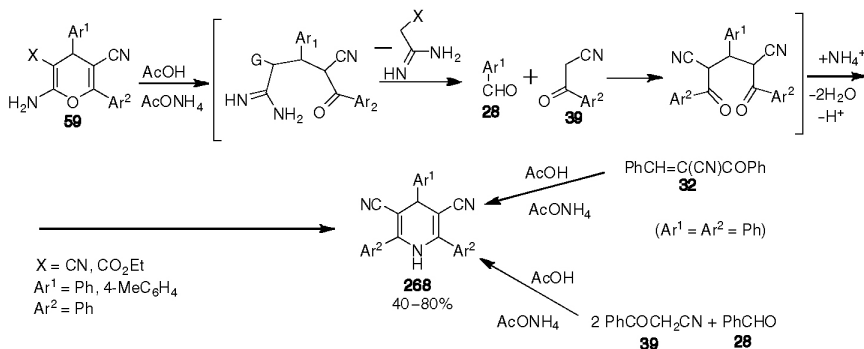
Scheme 106

of the cyano group leads to decomposition of the pyrans to aromatic aldehyde **28** and cyanoacetophenone **39**. Two equivalents of the latter react with 1 equiv. of aldehyde **28** and 1 equiv. of ammonia with formation of 1,4-dihydropyridine **268**, which does not oxidize into the corresponding pyridine. The reaction can be considered as a particular case of a Hantzsch 1,4-dihydropyridine synthesis (98RCR393). The structures of **268** have been proven by independent synthesis from **39** and **28**, or unsaturated **32** (81JHC309) (Scheme 106).

Along with ammonium acetate, amines and hydrazines have been reacted with 2-amino-4H-pyrans (81JHC309, 95PJC371, 01T5591). Aromatic amines and benzylamine with pyran **83** yield the recyclization product **269**, which contains a carbamoyl group in position 3. However, hydrazines give **270**, resulting from condensation by an aldehyde group without recyclization (01T5591) (Scheme 107).
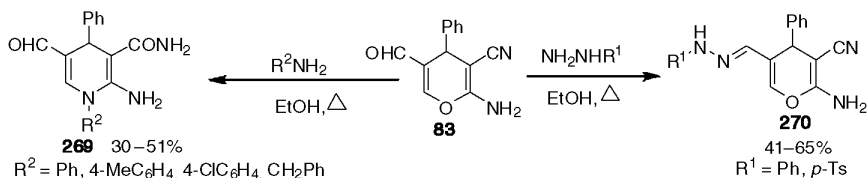
Scheme 107
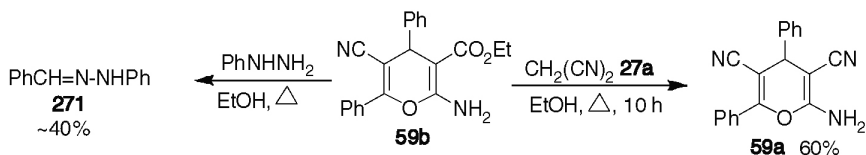
Scheme 108

Under the action of phenylhydrazine or 5-amino-3-phenylpyrazole on pyran **59b** only benzaldehyde phenylhydrazone **271** is formed, probably, as the result of pyran retro-cleavage (82M53). A similar reaction with malononitrile, leading to pyran **59a**, a product of formal "displacement" of a cyanoacetic moiety, possibly results from a similar cleavage (82M53) (Scheme 108).

An interesting transformation of pyran **22** into pyranopyrazole **193** has been observed with **22** and hydrazine hydrate or pyrazolone **194** (86ZNB925, 06MI1, 07MI1, 09MI1) (Scheme 109). Formal "displacement" of a carbethoxyethylene fragment by pyrazolone can be explained in terms of a retro-Michael cleavage followed by cyclization of UN **30** with pyrazolone, present or generated in the reaction medium (Scheme 109).

These mechanistic considerations led to the design of a four-component pyranopyrazole synthesis (09RCB2362, 09JCO914).

Attempts to obtain pyrano[3,2-d]pyrimidine **272** from guanidine and the corresponding pyrans failed. The products were diaminopyrimidines **273**, products of recyclization (86JPR35) (Scheme 110).

The mechanistic scheme proposed is similar to that in (81JHC309). Aromatization at the expense of disproportionation is also confirmed by the moderate yields. There are many examples of retro-cleavage of 2-amino-4H-pyrans into starting ketones and nitriles by the action of diverse reactants. They illustrate the reversible formation of a pyran ring in 2-aminopyrans.

Scheme 109

$Ar^1, Ar^2 = Ph, 4\text{-}MeC_6H_4, 4\text{-}MeOC_6H_4$
$X = CN, CO_2Et$

273 20–50%
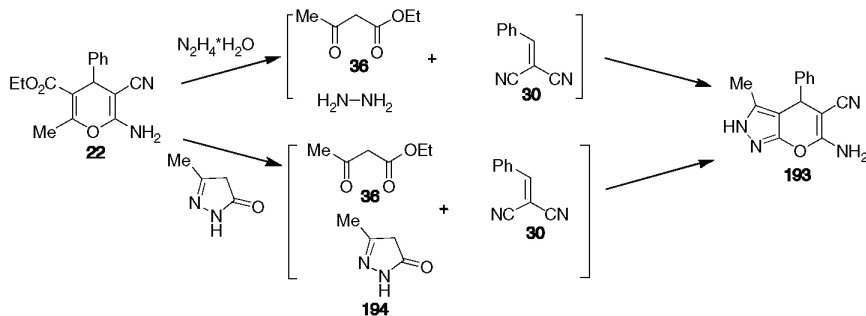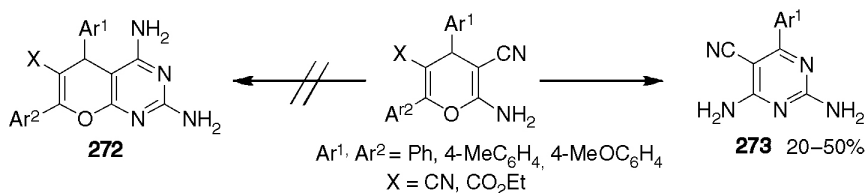
Scheme 110

The reactions of 2-amino-4*H*-pyrans with electrophilic agents represent another significant type of 2-aminopyran reactivity. These involve the amino group and make possible synthesis of various N-substituted 2-aminopyrans or fused pyrans. Pyran ring is not affected. Noteworthy, the amino group of 2-aminopyrans possesses much lower nucleophilicity compared with aliphatic amines, due to its conjugation with an electron-withdrawing substituent in position 3, as well as with its location at the C-2 carbon bonded to the oxygen (properties of NH_2 become similar to those of similar to a "cyclic amide"). For confirmation of its structure, pyran **18** was subjected to reaction with 4-methylbenzaldehyde and mixed formic-acetic anhydride. Like other primary amines, pyran **18** formed an imine **274** and formamide **275** (90CCC718), but these reactions required as much as 6–16 h for completion (Scheme 111).

To increase the stability of potentially antirheumatic pyran **143** toward acids, two analogs, bearing 2-*N*-pyrrolo- **276** and 2-succinimido **277** groups, were prepared by conventional methods (95BML2783) (Scheme 112).

For the same goal, in attempts to render 2-aminochromenes **278** and **279** acid-resistant, the 2-amino group was transformed into a ureide with

Scheme 111

Scheme 112

Ar = 3-Br-4,5-(MeO)$_2$C$_6$H$_2$
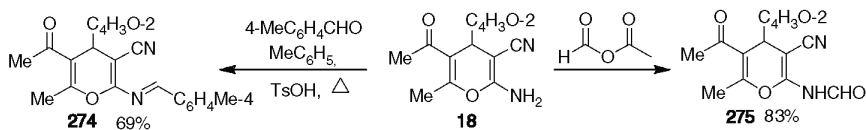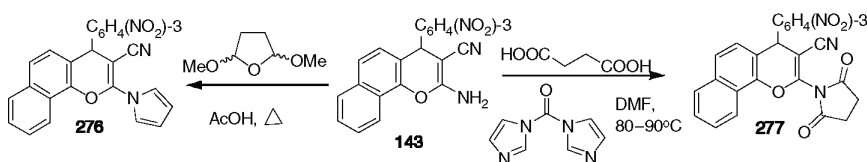
Ar = 3-Br-4,5-(MeO)$_2$C$_6$H$_2$
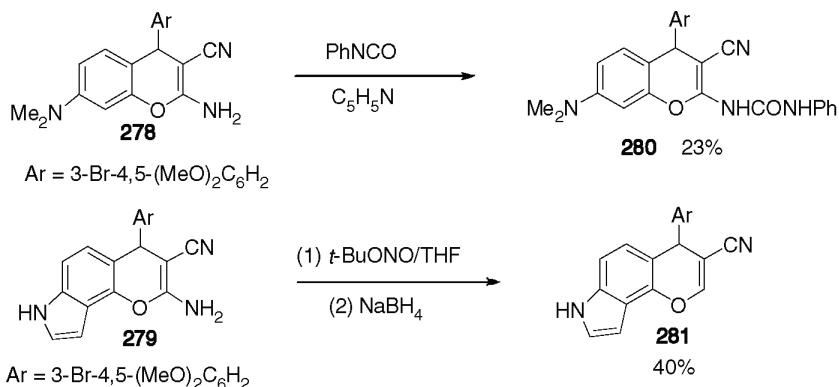
Scheme 113

phenylisocyanate (**280**) or the amino group was removed via reductive diazotization (**281**) (08BML603) (Scheme 113).

Acylation and imidoester formation were studied more extensively. Among aminopyrans, subjected to acylation there are nonannulated pyrans (86JPR35, 90CCC718, 08RCB2223), chromenes (08RCB2223), naphtho [2,1-*b*]pyrans (04MI2), 5,6-dihydronaphtho[1,2-*b*]pyrans (82M53), tetrahydrochromenes (08RCB2223), pyrano[3,2-*h*]quinolines (91BCJ668), pyrano [3,2-*c*]coumarines (03MOL275, 08RCB2223), and spiro(indeno[1,2-*b*] pyran-4,3′-indoles) (08H(75)955). Acetyl- and benzoylchlorides were employed (04MI2) as acylating reagents; as also, chloroacetyl chloride and 2-furoylchloride (03MOL275), *N*-acetylpyridinium chloride (94JHC749), and even acetonitrile in the presence of gaseous hydrogen chloride (02FA715, 04MI2) were used. But the most common reactant is acetic anhydride (86JPR35, 90CCC718, 91BCJ668, 03MOL275, 04MI2) or its combination with pyridine (91BCJ668, 95TA255, 08H(75)955). Here *N*-acetyl derivatives **282** or products of their cyclization, pyrano[2,3-*d*]pyrimidines **283**, are formed (Scheme 114).

Often it is difficult to predict the preferred product, basing on the literature. Since structures **282** and **283** are isomers, their identification is complicated. For example, in 86JPR35 the products of pyran acylations are
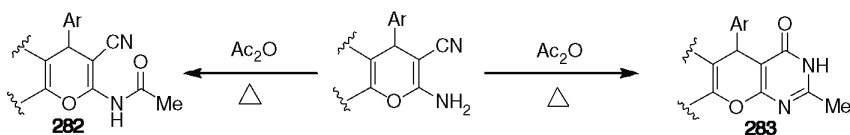
Scheme 114
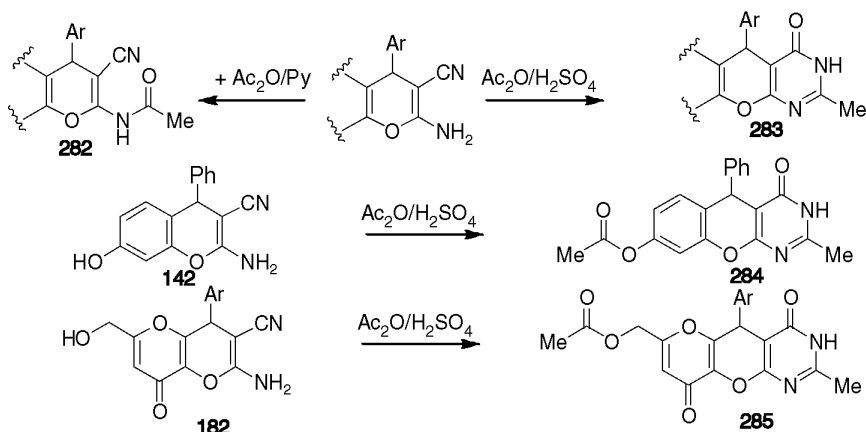
Scheme 115

pyranopyrimidines **283** according to the spectral data. However, they have been erroneously attributed to be 2-acetylaminopyrans. Usually, these reactions are carried out by long refluxing and are accompanied by formation of copious amounts of tarry products. To avoid side products and to shorten reaction time, the introduction of catalytic amounts of H_2SO_4 was suggested (08RCB2223). Heating periods now are several minutes, and the yields of **283** are good. Reactions with pyrans **142** and **182**, possessing OH-substituents, are accompanied with *O*-acetylation to give **284** and **285** (Scheme 115). Acetic anhydride combined with pyridine tends to give acyclic products **282** (Scheme 115).

Analogously, 3-carbethoxypyrans **104** in acid-catalyzed acetylation afforded oxazines **286** (09RCB479) (Scheme 116).

The other widely used transformation involves the action of ethyl orthoformate on 2-aminopyrans, yielding imidoesters **287**, which can be used in subsequent heterocyclizations (Scheme 117).

The reaction was studied on nonannulated aminopyrans (89M1101), tetrahydrochromenes, naphtha[2,1-*b*]pyrans (04MI2), pyrano[3,2-*h*]quinolines (91BCJ668), pyrano[3,2-*c*]coumarines (01MOL519, 03MOL275), and
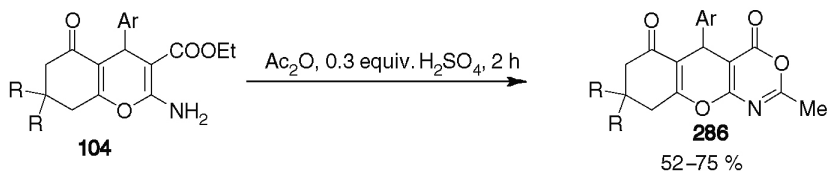
Scheme 116
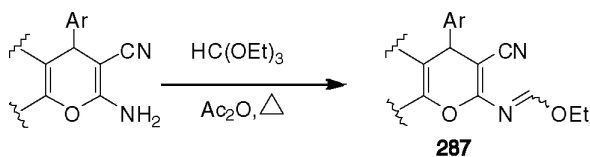
Scheme 117

pyrano[3,2-*c*]pyrazoles (90S704). Imidoesters obtained thereby easily react with N-nucleophiles in various ways, depending on the number of substituents at the N atom. Thus, dimethylamine only displaces the ethoxy group (91BCJ668, 99H(51)2765). Ammonia (89M1101, 02FA715, 04MI2), methylamine (91BCJ668, 02FA715, 04MI2), hydrazine (91BCJ668, 97JOC6575, 01MOL519, 02FA715, 04MI2), and semicarbazone (02MI1) also form the products of substitution, which immediately undergo cyclization to pyranopyrimidine **288** or **289** without isolation (Scheme 118).

A one-stage synthesis of aminopyrimidine **288a** or pyrimidone **288b** can be performed using ethoxymethylenepyrans with $HCONH_2$ and HCOOH, respectively (89CCC1336, 91BCJ668, 02FA715, 03MOL275) (Scheme 119).
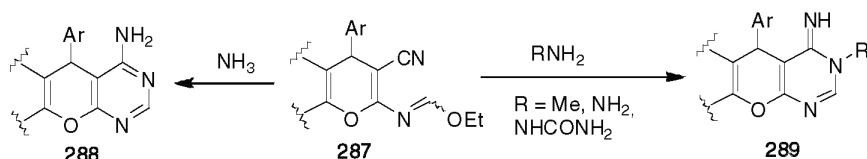
Scheme 118
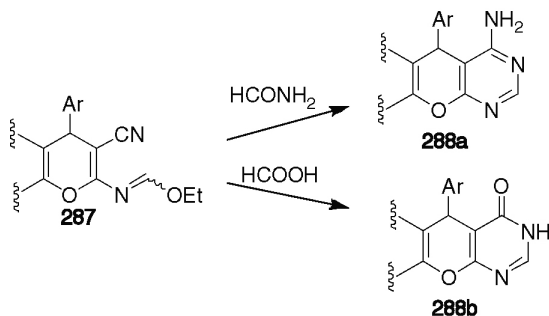
Scheme 119
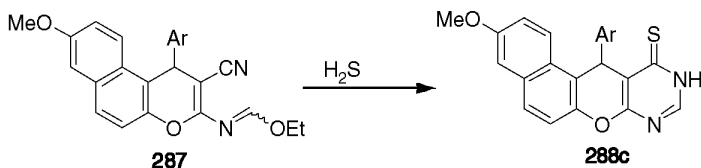
Scheme 120

These heterocyclic systems were in some cases subjected to further transformations (90S704, 01MOL519, 04MI2). Pyrimidinethione **288c** was reported as the result of treatment of **287** with H$_2$S (04MI2) (Scheme 120).

Addition of isothiocyanates to 2-amino-4H-pyran-3-carbonitriles with subsequent cyclization affords pyrano[2,3-d]pyrimidinethiones-2 **290** (89JPR971, 08PS1145) (Scheme 121).

Naphtho[2,1-b]pyrans **291** with carbon disulfide lead to dithiones **292** (08PS1145), perhaps via a Dimroth rearrangement of possible intermediates **293** (Scheme 122).

The classical variant of Friedländer reaction involves the reaction of *ortho*-acylarylamines with α-methylene carbonyl compounds (09CRV2652). 2-Aminopyran-3-carbonitriles, being similar to *ortho*-cyanoarylamines, were used instead of *ortho*-acylarylamines under modified Friedländer conditions (97BML3165). The enaminonitrile moiety of nonannulated pyrans **22** has been utilized for the synthesis of 4H-pyrano[2,3-b]quinolines **294**, analogs of tacrine in which the pyran ring serves as the benzene ring of tacrine. Subsequently, ketones with five- to seven-membered rings were used, as well as a variety of pyrans with different aryl and

Scheme 121

Ar = Ph, 4-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 2-O$_2$NC$_6$H$_4$, 2,4-(MeO)$_2$C$_6$H$_3$
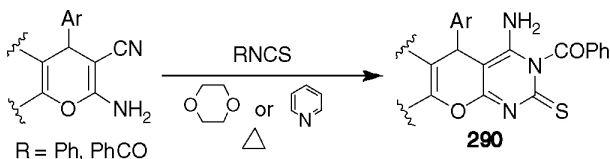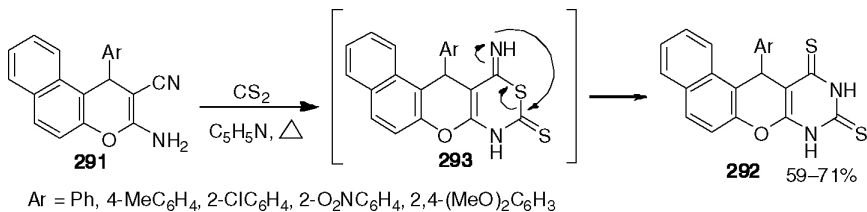
Scheme 122

Ar = Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$, 3-O$_2$NC$_6$N$_4$, 4-O$_2$NC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_4$, 2-(1-MeCO-)C$_4$H$_3$N, 2-C$_4$H$_3$O, 2-C$_4$H$_3$S, 3-C$_5$H$_4$N, 4-C$_5$H$_4$N;   R = Et, Pr^i

Scheme 123

X = H, 4-F, 2-CF$_3$, 3-NO$_2$, 4-NO$_2$, 4-Me, 2-MeO, 3-MeO, 4-MeO
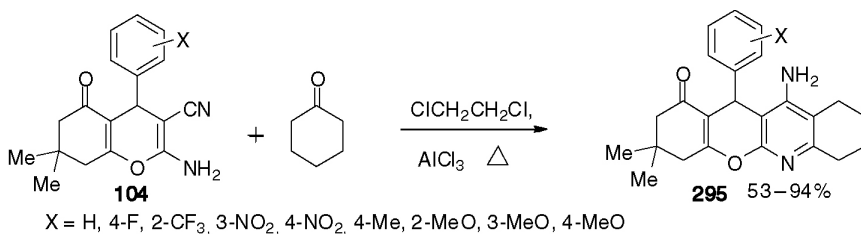
Scheme 124

carbethoxy substituents (01BML727, 02BML2077, 04BMC2199, 05BMC1167) (Scheme 123).

Tetracyclic tacrine analogs **295** were obtained from tetrahydro-4*H*-chromenes **104** (06BMC8176) (Scheme 124).

In contrast to the reactions of pyrans with electrophiles and nucleo-philes, oxidations of 2-amino-4*H*-pyrans are represented by very few examples. Oxidizing of **281** into 2-iminopyrans **296** with chloranil or dichlor-odicyanoquinone (DDQ) (04JME6299) can be used to protect the amino group in Sandmeyer reaction (**297**), or to introduce a methyl group into position 4 of pyran **298**. The latter is essential because the corresponding acetophenones do not give **298** with MN and aminophenols (Scheme 125).
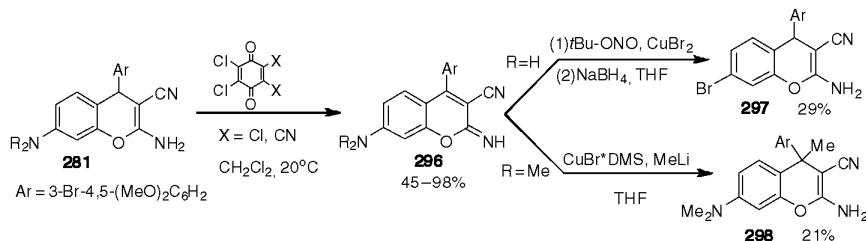
Scheme 125
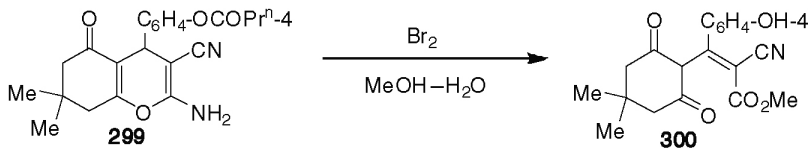
Scheme 126

One of the more unusual examples of oxidation with opening of the pyran ring involves **299** and methanolic bromine accompanied by hydrolysis of the ester group to yield acrylic acid **300** (04RJC1463) (Scheme 126).

5. PRACTICAL SIGNIFICANCE OF 2-AMINO-4*H*-PYRANS

2-Amino-4*H*-pyrans draw the attention of medicinal chemists. A substantial number of papers are devoted to assays for antibacterial (01MOL519, 02FA715, 03MOL275, 04MI2, 05BML4295), fungicidal (88JIC277, 91EJM221, 02FA715, 03MOL275), herbicidal (88JIC277), and molluscicidal activities (06AP456, 07AP543) of 2-aminopyrans. Fluorinated spiro-conjugated pyranopyrimidines (88JIC202) reveal anticonvulsant and analgesic activity (*in vivo*, using inbrend mice and albino rats). 2-Amino-4*H*-pyrans are isosters of 1,4-dihydropyridines, which reveal hypotensive activity at the expense of calcium channels modulation (85CPB3787). However, on comparison with highly active 1,4-dihydropyridine **301a** (X = NH, maximum hypotensive activity in rats: −82 mmHg, duration 8–24 h at 10 mg/kg), pyran analog **301b** (X = O) was completely inactive (85CPB3787).

301a,b

X = NH (**a**), O (**b**)
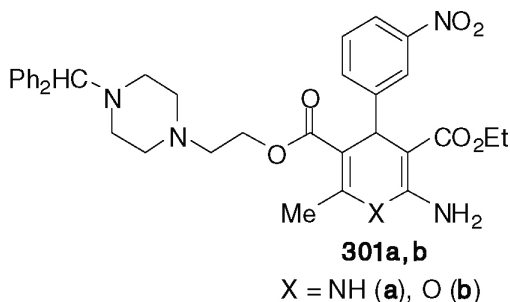
Nonannulated aminopyrans **22** and tetrahydrochromenes **104** were used in the synthesis of heteroanalogs **294** and **295** of tacrine **302**, a cholinesterase inhibitor applied in Alzheimer's disease treatment (01BML727, 02BML2077, 04BMC2199, 05BMC1167, 06BMC8176).
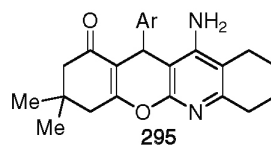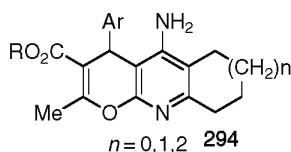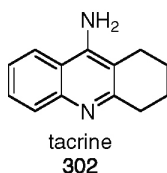
tacrine
302

$n = 0,1,2$ **294**

Ar = Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$, 3-O$_2$NC$_6$N$_4$, 4-O$_2$NC$_6$H$_4$,, 4-MeC$_6$H$_4$,
2-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3,4$^-$(MeO)$_2$C$_6$H$_4$, 2$^-$(1-MeCO$^-$)C$_4$H$_3$N,
2-C$_4$H$_3$O, 2-C$_4$H$_3$S, 3-C$_5$H$_4$N, 4-C$_5$H$_4$N; R = Et, *i*-Pr

295

Assays of acetyl- and butyrylcholine esterases inhibition, as well as of modulation of calcium channels and nicotinic receptors have been conducted *in vivo*. Moreover, their interaction with the active center of acetylcholine esterase has been simulated by molecular dynamics. For synthesized compounds the IC$_{50}$ of acetylcholine esterase inhibition was about 9×10^{-7}–10^{-5} M, and for the most active the value was four to five times higher than that of tacrine (1.8×10^{-7} M). Compounds **294** and **295** have also revealed neuroprotective activity.

Among the fused aminopyrans, 2-amino-4*H*-chromenes draw especial attention due to their broad biological potential. Benzochromenes **143** *in vitro* inhibit the synthesis of metalloproteases that destroy cartilage tissues in rheumatoidal arthritis and osteoarthritis. Moreover, **143** inhibit proliferation of mice spleen cells (95BML2783).
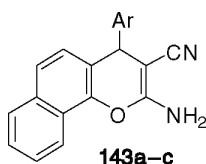
Ar = 3-O$_2$NC$_6$H$_4$ (**a**),
3-Cl-4-F-C$_6$H$_3$ (**b**),
3-C$_5$H$_4$N (**c**)

143a–c

Analogs **280** of **143** are more stable in acidic media, and retain their activity *in vitro*, and reveal *in vivo* antirheumatic activity (Lewis rats) (95BML2783).
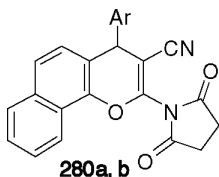
Ar = 3-O$_2$NC$_6$H$_4$(**a**),
3-C$_5$H$_4$N (**b**)

280a, b

Chromene **143c** (code LY290181) is a powerful inhibitor of cell proliferation, causing 50% of growth inhibition of cells of smooth vascular muscle, endothelial, Chinese hamster ovary, HeLa, and human

erythroleukemia cells at concentrations of 8–40 nM (97MI1). LY290181 binds with tubulin (at sites differing from colchicine and vinblastin) and destroys the formed microtubes of mitotic spindle, and, consequently, arrests mitosis at different stages, depending on its concentration (97JBC7681, 97MI1). LY290181 and its analogs inhibit the synthesis and secretion of metalloproteases from chondrocytes (95MI1). Possessing anti-proliferative activity, LY290181 provides significant inhibition of smooth muscle cell proliferation and arterial intimal thickening after balloon angioplasty when administered systematically (96MI1).

Extensive SAR studies of 2-amino-4*H*-chromenes search for molecules with high anticancer activity (04JME6299, 04MI4, 04MI5, 05BML4745, 07JME2858, 08BML603, 08JME417). Studies with chromenes on cell growth inhibition (GI_{50}), together with activation of caspases (cysteine proteases, playing a substantial role in apoptosis) (EC_{50}), have been performed. For the EC_{50} assays a series of human cells has been used: breast cancer cells T47D, colon cancer cells DLD-1, nonsmall cell lung cancers H1299, colon cancer cells HCT116, and hepatocellular carcinoma cancer cells SNU398. As a rule, GI_{50} and EC_{50} correlated well, that is, the substances, which activate caspases the best, are also the most active in the inhibition of cell culture proliferation assays. Therefore, mainly EC_{50} values are given in Table 3.

Studies on lead optimization have been conducted in the following order:

- Modifications of a 4-aryl substituent (04JME6299).
- Modifications of substituents in chromene 5–8-positions (05BML4745).
- Modifications of the ring conjugated with a chromene ring at positions 7 and 8 (07JME2858).
- Modifications of a five-membered ring, conjugated with a chromene ring at positions 7 and 8 (08JME417).

Dozens of compounds have been studied, resulting in structures, which possess EC_{50} values about 1–5 nM. Compounds **281**, **282**, **303–308**, which revealed the highest activity at each optimization stage and played a key role in the studies, are listed in Table 3.
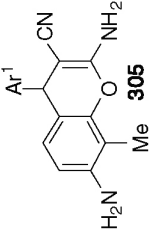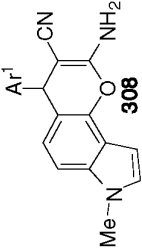
To provide greater tolerance toward acids for compounds **303–308** and others, (08BML603), the substituents in positions 2 and 3 were modified. Substitution of ester groups for a nitrile led to a 200-fold drop in activity. Changing an amino group into a succinimide or NHCONHPh group (**283**) reduced the activity 4- to 10-fold. 2-Unsubstituted compounds **284** and **309**, synthesized via reductive diazotization of the corresponding 2-aminochromenes, reveal relatively high activity (about 30–60 nM) and selectivity. Their expected acid resistance can also positively influence their bioavailability.

Table 3. The key compounds in the structure optimization of 2-amino-$4H$-chromenes

Structure	EC$_{50}$ (nM)	References	Structure	EC$_{50}$ (nM)	References
281 Ar^1 = 3-Br-4,5-(MeO)$_2$C$_6$H$_2$	19–43	04JME6299	**282**	5–15	07JME2858
303 Ar^2 =	11–27	04JME6299	**306**	2–3	08JME417
304	14–27	05BML4745	**307**	1–4	08JME417

(continued)

Table 3 (*continued*)

Structure	EC$_{50}$ (nM)	References	Structure	EC$_{50}$ (nM)	References
305	26–53	05BML4745	**308**	2–3	08JME417

284
47−66 nM

309
29−38 nM
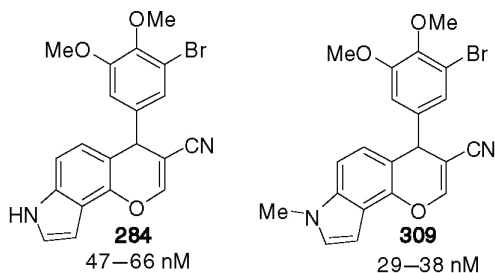
The mechanism of biological action of **281** has been thoroughly investigated (04MI4, 04MI5). These 2-aminochromenes reveal anticancer activity as the result of caspase activation, and, consequently, starting the apoptosis mechanism. However, somewhat different 2-amino-4*H*-chromenes **161** show antitumor activity by another mechanism, which involves inactivation of antiapoptotic proteins of the Bcl-2 series.

161a

161b−h

$R = $ H **(b)**, Me **(c)**, Et **(d)**, Pr^n **(e)**, Ph **(f)**, CH(CH$_2$)$_4$ **(g)**, 4-ButC$_6$H$_4$ **(h)**
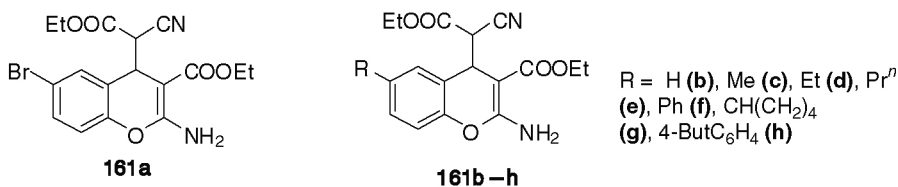
Chromene **161a** causes fast apoptosis of muscular leukemia cells L210 and is comparable to the action of photodynamic therapy, where their combined action increases apoptosis of cancer cells (02MI3). SAR studies of substituents at C6 (**161b−h**) have shown that compounds with alkyl (especially bulky) groups (**161h**) possess high affinity toward Bcl-2 proteins (06JME7731). A positive correlation between affinity toward these proteins and cytotoxicity has been found as well as a synergetic effect of **161** in *cis*-platine therapy in the cases of increased expression of antiapoptotic proteins Bcl-2 (06JME7731).

2-Amino-4*H*-chromenes reveal affinity toward estrogenic receptors ERα (07JME5301). Target-specific virtual screening of more than 200,000 compounds of various classes and subsequent biological assays found two new ligands **310a,b** with nanomolar activity (IC$_{50}$ 53–56 nM).

310a, b
Ar = 2-FC$_6$H$_4$ (**a**), 4-MeC$_6$H$_4$ (**b**)
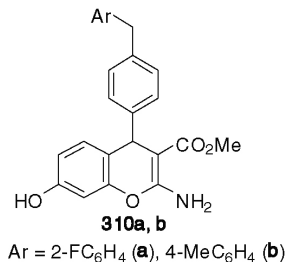
2-Aminopyrans, fused with heterocycles, also show high biological activity. Hydrogenated pyranopyridines **311** are active against several types of tumor cultures (00JME2915).

Ar = 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-C$_4$H$_3$S

311
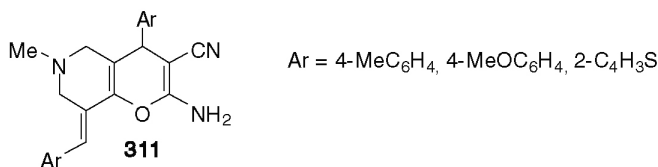
Pyranopyridines **179** and pyranoquinolines **185** are close to chromenes **281** in their mechanism of biological action. Compounds **179** and **185** at micro- and nanomolar concentrations (for the most studied compounds GI$_{50}$ was about 3–3000 nM) cause arrest of cells in the G2/M phase and inhibit tubuline polymerization (07BML3872, 08JME2561).

179   **185**
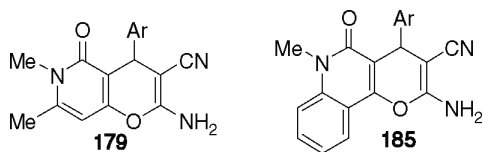
Ar = Ph,3-BrC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$, 3-HO-4-MeOC$_6$H$_3$, 3,4,5(MeO)$_3$C$_6$H$_2$, 3-Br-4,5(MeO)$_2$C$_6$H$_2$, etc.

Kinases Chk1 play a significant role in the regulation of the G2/M cell cycle, so inhibitors of kinases of this class are promising antitumor agents (06BMC4792). Docking with the ATP-binding site of Chk1 kinase has been performed for compound **312**, and the experimental inhibition value IC$_{50}$ is 20.4 ± 2.5 μM.

312
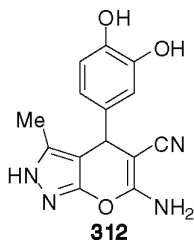
The 2-aminochromene moiety can influence the other types of biological activity. A series of pyrimidine nucleosides **313**, containing a 2-amino-5,6,7,8-tetrahydrochromene fragment, reveal activity against *Leishmania donovani* (06BML5047) (IC$_{50}$ about 1–10 μ).

Z = CN, COOEt
R = H, Me, 4-FC$_6$H$_4$

313
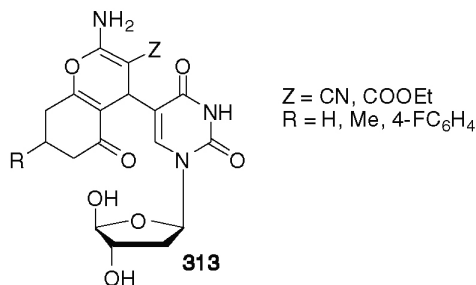
2-Amino-4*H*-pyrans represent a significant class of oxygen-containing heterocycles, whose high biological activity provides broad prospects for their practical applications.

LIST OF ABBREVIATIONS

EDG   electron-donating group
EWG   electron-withdrawing group
MN   malonodinitrile
mw   microwave field
PEG   polyethylene glycol
TCE   tetracyanoethylene
TEBAC   triethylbenzylammonium chloride
UCC   unsaturated carbonyl compound
UN   unsaturated nitrile

ACKNOWLEDGMENT

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