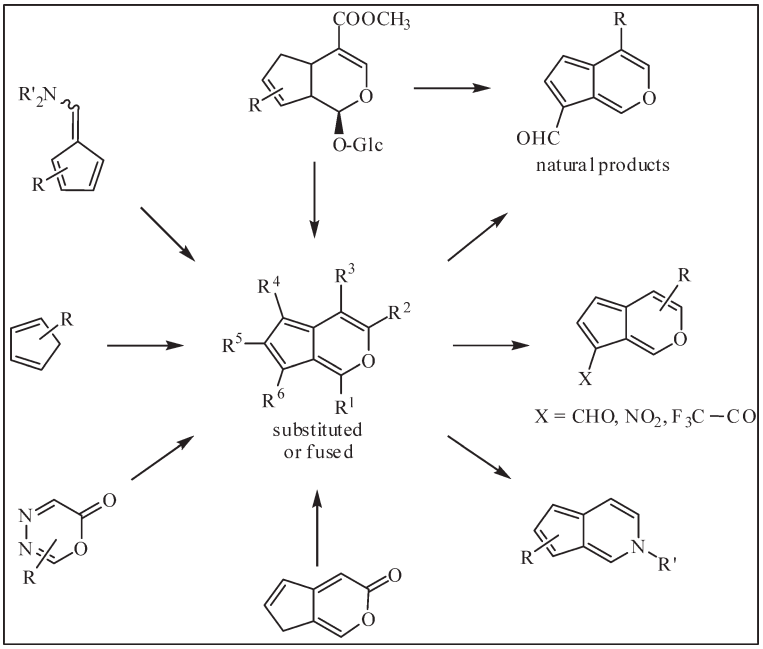
Mihaela Ţînţaş, Elena Bogdan,* and Ion Grosu

"Babes-Bolyai" University, Organic Chemistry Department and CCOCCAN,
Arany Janos 11, RO-400028, Cluj-Napoca, Romania
*E-mail: ebogdan@chem.ubbcluj.ro

Received March 11, 2010
DOI 10.1002/jhet.589
Published online 14 April 2011 in Wiley Online Library (wileyonlinelibrary.com).



Natural occurrence, synthesis, chemical behavior, and physical properties of aromatic cyclopenta[*c*]-pyrans are reviewed. Various strategies for the synthesis of cyclopenta[*c*]pyrans starting from cyclopentadienes, fulvenes, oxadiazinones, or α-pyrones were developed according to the substitution patterns of the target compounds.

J. Heterocyclic Chem., **48**, 747 (2011).

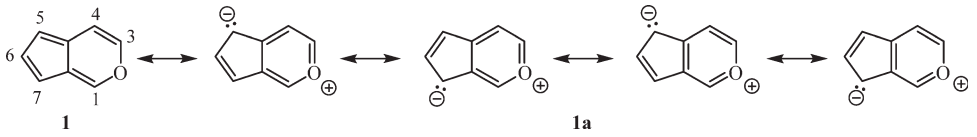
Contents

1. INTRODUCTION

Cyclopenta[*c*]pyrans are heterocyclic compounds structurally consisting of a cyclopentadiene fused to the *c*-bond of a pyran unit. They have a total number of 10 conjugated π-electrons including the lone pair of the oxygen atom.

The parent compound **1** (Chart 1) belongs to a large class of heterocycles, namely pseudoazulenes [1], which are π-isoelectronic analogues of the nonbenzenoid aromatic hydrocarbon azulene. Formally, pseudoazulenes result by replacing a vinylene group of azulene by a heteroatom, whose unshared electron pair ensures the aromatic character of the system.

Previously, oxygen-containing pseudoazulenes were named oxalenes [2] in accordance with the azulene naming, which linguistically expresses the structural analogy; yet, nowadays pseudoazulenes are named according to IUPAC rules.



1 **1a**

Chart 1

Similar to azulene, the dipolar resonance structures **1a** (Chart 1) contributes to the electron distribution of the ground state of cyclopenta[*c*]pyran, which shows an enhanced electron density in the five-membered ring and an electron deficiency in the six-membered one. This similarity suggests an analogy of the properties with those of azulene, foreshadowing the chemical behavior of the cyclopenta[*c*]pyran entity. However, there are only few reports dealing with the reactivity of cyclopenta[*c*]pyrans [3,4], showing strong preference of the electrophilic attack at 7- and 5-positions.

The cyclopenta[*c*]pyran system is well known as the subunit or the core of the natural products called Iridoids [5]. The majority of them are partially or fully hydrogenated cyclopenta[*c*]pyran monoterpenes, but there are several reports on compounds with the fully aromatic heterocycle. The name ''iridoids'' was given to the first members isolated from the secretion of ants belonging to the genus *Iridomyrmex*. In 1949, Pavan [6] obtained the lactone iridomyrmecin **2** (Chart 2), known to be an effective insecticide and having antibiotic activity, from the ant *Iridomyrmex humilis*.

The intriguing chemistry of the cyclopenta[*c*]pyran system raised our interest and, thus, we decided to summarize the literature findings concerning the isolation and the structural investigation of the natural products with an aromatic cyclopenta[*c*]pyran moiety, the developments in the synthetic approaches leading to cyclopenta[*c*]pyran and its derivatives and the results dealing with investigations of the aromaticity and the reactivity of this heterocyclic system.

2. NATURAL OCCURRENCE, ISOLATION AND BIOLOGICAL ACTIVITY

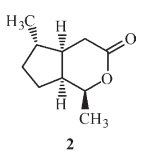
Iridoids are monoterpenes and they are often found as intermediates in the biosynthesis of alkaloids. Over 400 specimens have been isolated from terrestrial and marine flora and fauna only in the past 15 years [7]. Iridoids are secondary metabolites found in a large number of plant families, usually as glycosides. Attached to C-1, the β-glucoside group provides enhanced stability to the pyran ring. Having a partially or fully hydrogenated cyclopenta[*c*]-pyran skeleton, they attracted considerable attention due to their divers and important biological activities [5,8].

A central position among iridoids is held by loganin **3** (Chart 3), which was first isolated from *Strychnos nux vomica*. This monoterpene glucoside is important in plant biochemistry due to its role in the biosynthesis of indole alkaloids and other natural products [8,9]. Isolated from the *Valeriana Wallichii*, didrovaltrate **4** (Chart 3) is a very potent cytotoxic agent for the rat hepatoma cells, effectively inducing definitive remissions of the Krebs II ascitic tumors. Abundantly available by enzymatic hydrolysis of geniposide, extracted from *Gardenia jasmidones*, (+)-genipin **5** (Chart 3) was used as the starting material for the synthesis of several iridoids of biological interest [8] (see section 3.1).

In the thick of the numerous monoterpene iridoids reported, a smaller number of natural compounds possessing an aromatic cyclopenta[*c*]pyran system have been isolated and identified. They can be considered as a subclass of the iridoids with particularly interesting properties and behavior.

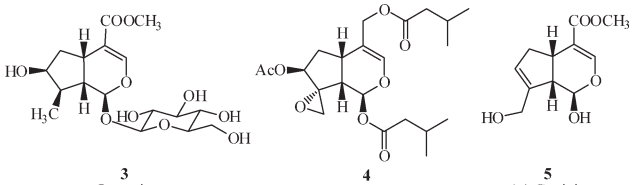
Up till now, the number of aromatic cyclopenta[*c*]pyrans obtained as natural compounds or degradation products of nonaromatic natural precursors has raised to seven: baldrinal (and its analogs homobaldrinal, desacylbalbrinal, 11-methoxyviburtinal, 11-ethoxyviburtinal), viburtinal, norviburtinal, halitunal, cerbinal (and its relatives cerberic acid and cerberinic acid), fulvoipolamiide, and torricellate. Most of these compounds bear an aldehyde functionality at C-7 conferring stability by its electron withdrawing effect.

Heretofore, the unsubstituted cyclopenta[*c*]pyran **1** (Chart 1) has not been found as a natural product, which may be due to its high reactivity. In spite of this, the mentioned derivatives were isolated, characterized, and



2
Iridomyrmecin

Chart 2



3 **4** **5**
Loganin Didrovaltrate (+)-Genipin

Chart 3

tested with regard to their biological activity, as it has been found in case of the partially or fully hydrogenated cyclopenta[*c*]pyran specimens.

Reported by Thies in 1968 [10], the first aromatic cyclopenta[*c*]pyran iridoid was the yellow-colored baldrinal **9** (Chart 4), isolated as product of the acidic work-up of valtrate **6** (Chart 4) from the rhizomes and roots of *Valeriana wallichii* D.C. It was also found in a small quantity in the roots of *Valeriana jatamansi* among other components [11]. Valerians (or *Valerianaceae*), known to contain compounds with pharmacological activities, can be used as herbal medicine (or ''dietary supplements'' [12]) in the form of capsules, extracts, infusions, tinctures, plant juice, and tea [13]. A notable class of their chemical constituents is called Valepotriates, which are epoxy iridoid esters, considered to be responsible for sedative and cytotoxic effects. They are very unstable thermally and in strongly acidic as well as strongly basic medium [14,15]. Baldrinal **9** was identified as a degradation product of the diene-valepotriates valtrate **6** and acevaltrate **8** under acidic conditions (Chart 4), while homobaldrinal **10** emerges from isovaltrate **7** [14–16]. Many investigations of the biological properties, such as the mutagenic effect on *Escherichia coli* and *Salmonella*, the cytotoxicity against GLC_4 (human small-cell lung cancer cell line) and against COLO 320 (human colorectal cancer cell line), the genotoxicity, the reproduction and biochemical changes in male mice, revealed only a reduced of the expected phytotherapeutic activity of **9** and **10** compared with their parent valepotriates [14,17–19]. However, **9** was found to exhibit a potent cytotoxicity *in vitro* against HTC hepatoma cells and anti-tumor activity *in vivo* against KREBS II ascitic tumor [8].

Hydrolysis in weak alkaline media leads to the loss of the acyl groups of baldrinal **9** and homobaldrinal **10** with formation of the corresponding alcohol desacylbaldrinal **11** (Chart 4), which was investigated for sedative properties [15,16].

Cerbinal **12** (Chart 5), a yellow pigment, was isolated from the bark of *Cerbera manghas* L. along with its relatives cerberic acid **13** (Chart 5) and cerberinic acid **14** (Chart 5) in 1977 [20]. After purification by chromatography on silica gel, the structures were investigated by UV-vis and NMR spectroscopy as well as mass spectrometry and additional proves were achieved by oxidation of **12** with CrO_3 in acetic acid with formation of **13** and methylation of **14** by diazomethane to give **12**. Treatment of theviridoside, one of the main iridoid constituents found in the leaves of the tree *Cerbera manghas* L., with Jones reagent afforded among other products a small quantity of cerbinal **12**.

Based on the fact that **12–14** were extracted from the leaves or bark of old trees and not from those of young trees, which are rich in theviridoside, the authors [20] conclude that **12–14** have to be considered as genuine natural products rather than degradation products as in case of baldrinal **9**.

In 1986, the nonglycosidic iridoid cerbinal **12** was also isolated from *Gardenia jasminoides* Ellis, and the authors believed that **12** itself is not contained in the intact fresh leaves but formed by the action of certain enzymes [21] on standing one day at room temperature in benzene or methanol. By employing various conditions and the same solvents, no **12** was found on immediate extraction, which supports the above assumption. Cerbinal **12** was reported to show antifugal activity against *Bipolaris sorokiniana, Helminthosporium, Pyricularia, Colletotrichum lagenarium,* and *Puccinia* species. At concentrations of 0.75–4 μg/mL, **12** caused the germination of spores of *Puccinia* species on oat, wheat, Welsh onion and white clover to be inhibited to 100%. Interestingly, both plants *Cerbera manghas* L. and *Gardenia jasminoides* Ellis are used as traditional medicinal herbs.

The unusual pseudoazulene iridoid structure is also present in viburtinal **15**, norviburtinal **16** and halitunal

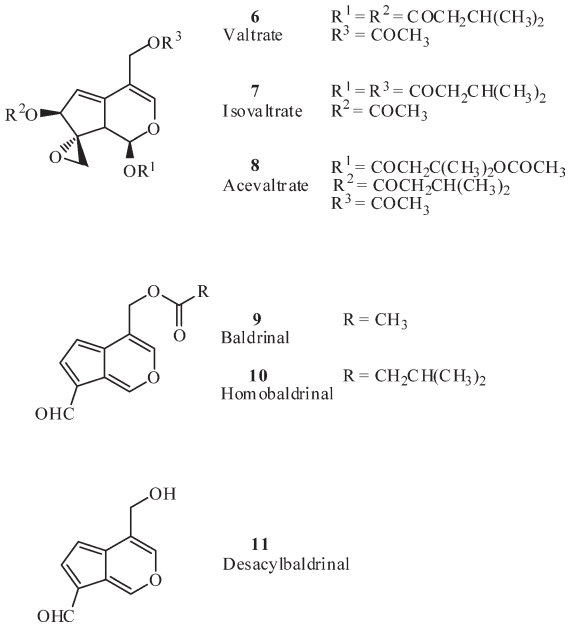


Chart 4

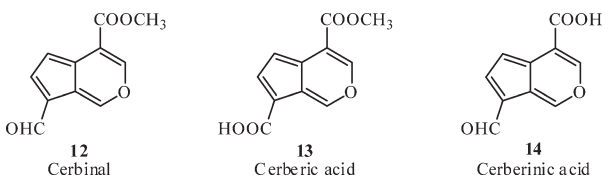


Chart 5

17 (Chart 6). Viburtinal **15** was isolated from the leaves and bark of *Viburnum tinus*, *Viburnum opulus,* and *Sambucus* (Caprifoliaceae) [22–24]. *Virbunum* bark and dried leaves have been traditionally used in indigenous medicine in the treatment of internal bleedings, and also possess spasmolytic, cardiotonic, and sedative properties [23]. As in cases of baldrinal **9** and cerbinal **12**, **15** was obtained as decomposition artifact after extraction of the alloside iridoids by acid hydrolysis with 10% hydrochloric acid in methanol.

Norviburtinal **16** (Chart 6), the simplest cyclopenta[*c*]pyran iridoid isolated, was directly obtained as a yellow-orange solid by the extraction of the root bark of *Kigelia pinnata* [25] with benzene and later by the extraction the stem bark of *Stereospermum personatum* [26] with chloroform. Both plants are members of the Bignoniaceae family. Extracts from *Kigelia pinnata*, colloquially called the Sausage Tree, were used by indigenous Africans for a wide rage of medicinal applications such as dysentery or venereal diseases but also as topical applications on wounds [27]. *Stereospermum personatum* is a traditional Indian medicinal plant known for its diuretic and anti-inflammatory effects, used in treatment of hemorrhoids, vesical calculi, and also for cardiotonic, diabetic, cancer, renal, and hyperacidity diseases [26]. Norviburtinal **16** was found to be the most active compound from the crude extract with dichloromethane with respect to the cytotoxic activity *in vitro* against cultured melanoma but with little selectivity toward different melanoma cell lines [28].

Halitunal **17** (Chart 6), a novel diterpene aldehyde and the only chiral iridoid with a fully aromatic cyclopenta[*c*]pyran system, was isolated from the calcareous marine alga *Halimeda tuna* after repeated extractions with methanol/toluene and *n*-butanol followed by HPLC on C_{18} column and subsequently on silica gel [5,29]. Its absolute configuration is still unknown, although both enantiomers were synthesized (see section 3.1), because a comparison with a natural sample was not possible [30]. Halitunal **17** was reported to show *in vitro* antiviral activity against murine coronavirus A59.

11-Methoxyviburtinal **18** (Chart 6) was isolated from *Valeriana jatamansi*, a plant widely used in Chinese traditional medicine due to its hypnotic, tranquilizing, and antiviral activity [11]. In the ethanolic extract of the plant roots, baldrinal **9** was also found among other major components. The authors considered the newly discovered iridoid **18** as a degradation product like baldrinal **9**.

Another member of the pseudoazulene iridoids, 11-ethoxyviburtinal **19** (Chart 6), which is the ethyl ether of desacylbaldrinal **11** (Chart 5), was isolated from the ethanolic extract of the roots of *Centranthus ruber* (L.) D.C. [31].

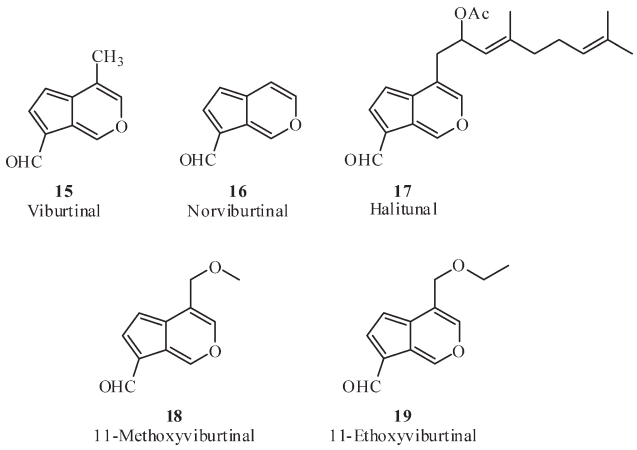


Chart 6

Except cerberic acid **13**, all iridoids with a fully aromatic cyclopenta[*c*]pyran system described above possess an aldehyde functionality, which may play a major role in their biological and pharmacological activities.

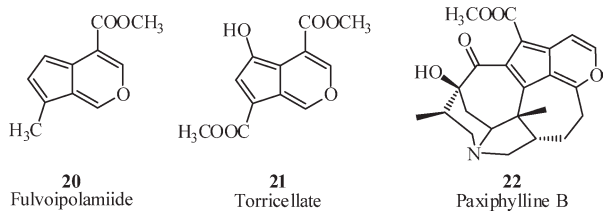
Fulvoipolamiide **20** (Chart 7) was obtained as an orange-red solid from the aglycone of ipolamiide in 1976 [32] and directly isolated from the dried leaves of *Stachytarpheta glabra* (Verbenaceae) by hydrodistillation extraction in 2008 [33]. Most probably, ipolamiide was degraded to the stage of **20** in the latter procedure as well. Although no biological activity of **20** was proved until now, increasing interest was recorded when previous reports on isolation of lamiide and ipolamiide iridoids from different species of *Stachytarpheta* pointed out antimicrobial, antitumoral, anti-inflamatory, and hepatoprotective activities.

The most recently discovered iridoid with a cyclopenta[*c*]pyran skeleton, torricellate **21** (Chart 7), was isolated from the fresh root bark of *Torricella angulata* var *intermedia* (Torricelliaceae), a plant used in Chinese traditional medicine to treat bone fracture, tonsillitis and asthma [34].

Even if it is not an iridoid, paxiphylline B **22** (Chart 7), an alkaloid isolated from the twigs and leaves of the *Daphniphyllum paxianum* tree [35], has incorporated in its structure a cyclopenta[*c*]pyran unit. The compound **22** was obtained as an optically active light yellow solid and its structure was analyzed by IR, NMR, and UV-vis spectroscopy as well as high resolution mass spectrometry. A cytotoxicity assay showed that it was not active against the acute myelogenous leukemia or human lung cancer cell lines.

3. SYNTHESIS

The increasing number of cyclopentanoid natural products and their interesting, wide-range biological



20 Fulvoipolamiide **21** Torricellate **22** Paxiphylline B

Chart 7

activity has stirred considerable interest into the synthesis of such compounds. The broad diversity of both, structure and biological activity, exhibited by iridoids and secoiridoids, has generated much interest in their general synthesis [5].

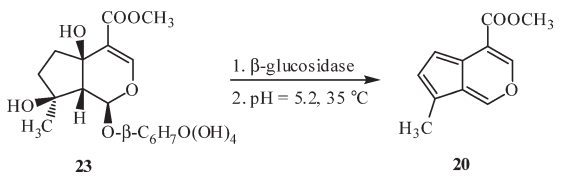
Herein are presented the methods of synthesis targeted to the preparation of naturally occurring compounds and various strategies used to prepare the parent compound cyclopenta[*c*]pyran and its derivatives. Problems like the sensitivity to air, oxygen, acidic, or alkaline media make the synthesis of this peculiar 10π aromatic system a continuous challenge for chemists.

3.1. Natural products. The total synthesis of cyclopentanoid monoterpenes such as the iridoids [5,36–38] has been the objective of many research works over the last four decades because of the biological activity and structural interest.

The synthesis of fulvoipolamiide **20** [32] is based on the readily occurring hydrolysis of glucosides. By enzymatic hydrolysis (β-glucosidase) in phosphate buffer, ipolamiide **23** was converted into its aglycone, which gave rise to **20** on warming at 35°C in aqueous solution at pH 5.2 for several hours (Scheme 1).

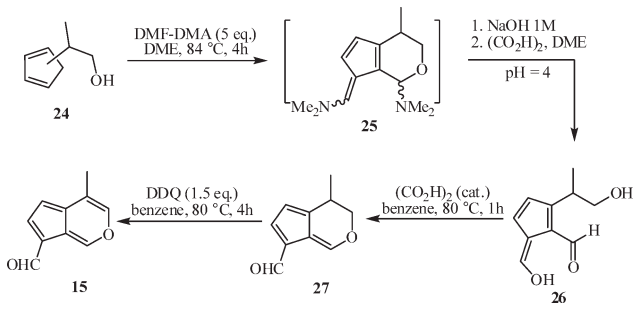
The synthesis of viburtinal **15** was reported as a sequence of reactions (Scheme 2) starting from the cyclopentadienylpropanols **24** (tautomeric mixture) [39]. Treatment of **24** with an excess of dimethylformamide dimethyl acetal (DMF-DMA) led to the unstable aminofulvene **25**, which was hydrolyzed in alkaline medium. The resulting product was immediately submitted to an acid-catalyzed hydrolysis [oxalic acid in 1,2-dimethoxythane (DME)] to give the hydroxyfulvene **26**. Subsequent cyclization furnished the dihydrocyclopenta[*c*]-pyran **27** in 30% yield (calculated from **24**), which finally was dehydrogenated by dichlorodicyanobenzoquinone (DDQ) to give the desired **15** in 55% yield.

Scheme 1



23 **20**

Scheme 2



24 **25** **26** **27** **15**

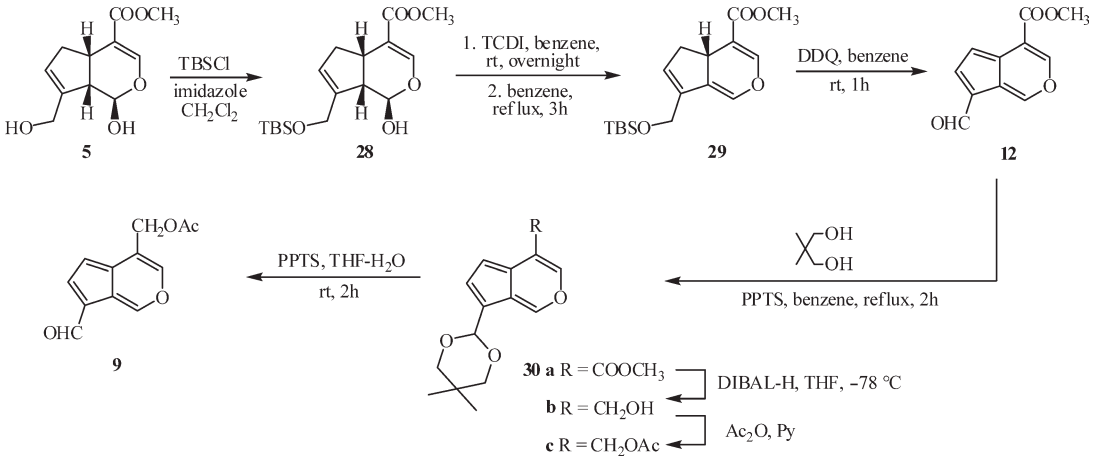
An effective utilization of (+)-genipin **5** (Scheme 3), easily obtained from water extracts of *Gardenia jasminoides* Ellis by enzymatic hydrolysis of geniposide, was reported by Isoe [8] for the synthesis of several polyfunctionalized iridoids. The use of (+)-genipin **5** as starting material enabled the synthesis of cerbinal **12**, baldrinal **9** and halitunal **17**.

The first synthesis of cerbinal **12** from (+)-genipin **5** proceeded over six steps in 24% overall yield [40]; it was later resumed in a more efficient protocol (Scheme 3) [8]. Silylation of **5** with *t*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazol quantitatively gave the monosilyl ether **28**. A subsequent dehydration with 1,1′-thiocarbonyldiimidazole (TCDI) in benzene led to an unstable thioimidazolide, which on heating in refluxing benzene afforded the dihydrocyclopenta[*c*]pyran **29**. The dehydrogenation of the heterocycle and the oxidation of the allylic carbon atom was achieved in one step with DDQ and furnished **12** in 37% overall yield.

Cerbinal **12** could be used for its part as the starting material for the synthesis of baldrinal **9** (Scheme 3). The acetalization to protect the formyl group of **12** was performed with 2,2-dimethyl-1,3-propandiol in high yield (88%) by using pyridinium *p*-toluenesulfonate (PPTS) as catalyst; this acid is weak enough to avoid the protonation of the cyclopenta[*c*]pyran moiety. Reduction of the ester group with diisobutylaluminium hydride (DIBAL-H) afforded the alcohol **30b** as key intermediate. Subsequent acetylation with acetic anhydride gave rise to the desired methyl acetate group at C-4 and, finally, liberation of the formyl group with a catalytic amount of PPTS furnished baldrinal **9**.

Also using (+)-genipin **5** as the starting material, Isoe *et al*. [30] took advantage of a similar strategy for the semi-synthesis of both enantiomers of halitunal **17** (Schemes 4 and 5). Although **17** contains only one stereogenic center, which is located in the side-chain (C-10; originally, the authors had incorrectly given the number 12 to this carbon atom), the chirality of **5** was used as a means for ensuring the purity of the 10-hydroxylated intermediates **34**.

Scheme 3



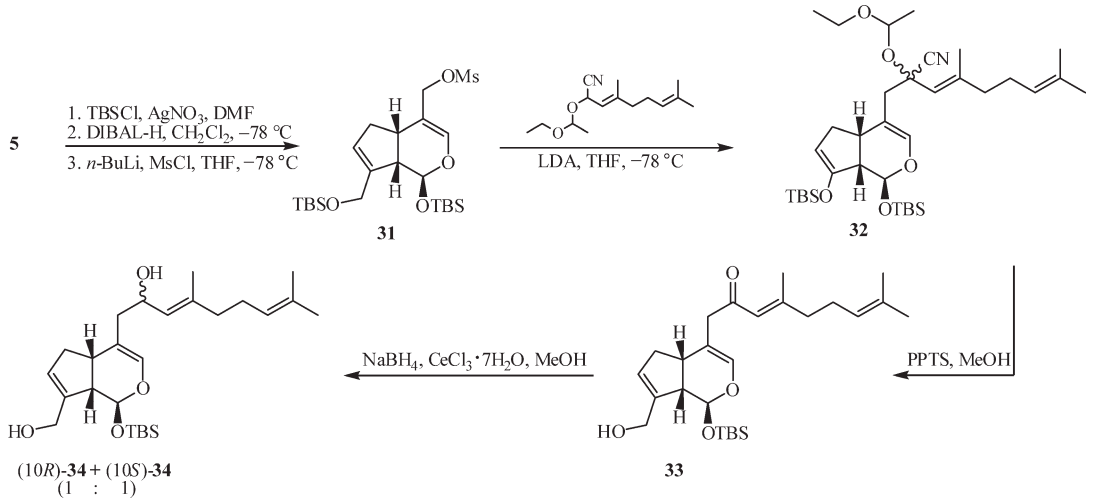
The side-chain was introduced by the substitution of the mesylate group of **31**, which was prepared in three steps from **5** and treated with the carbanion of 1-cyanogeranyl ethoxyethyl ether to give a 1:1 mixture of the diastereomers **32** (Scheme 4). The acid-catalyzed decomposition of **32** with formation of a ketone functionality proceeded concomitant with the selective removal of the primary silyl ether group and was followed by the reduction of ketone group. Each isomer of the resulting separable diastereomeric allylic alcohols **34** was converted into the corresponding optically pure enantiomer of halitunal **17** by successive dehydration and oxidation (Scheme 5).

The natural [29] and synthetic **17** had identical spectroscopic data, but the optical rotation was not available for the natural compound and, thus, the assignment of its absolute configuration still remains unknown.

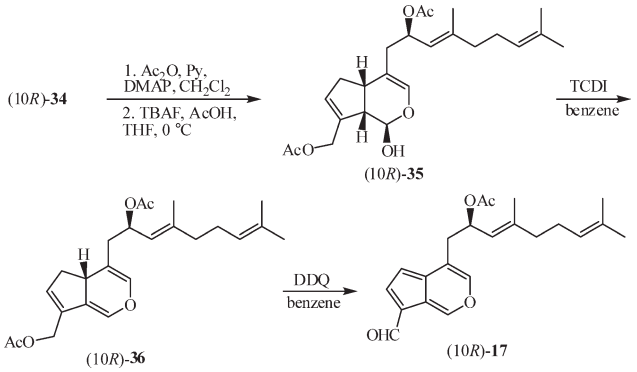
3.2. The parent heterocycle and non-natural derivatives. A general procedure of synthesis could not be elaborated yet, but several strategies starting from cyclopentadienes [41], fulvenes [42], oxadiazinones [4], and α-pyrones [3] have been developed for the preparation of the parent compound **1** and derivatives with various substitution patterns.

The first synthesis of a compound possessing the cyclopenta[*c*]pyran skeleton was reported by Harley-Mason and Harrison in 1963 [43]. On thermolysis of phenacyltrimethylammonium hydroxide, 1,2,3-tribenzoylcyclopropane resulted as the main product, but an intensively red colored by-product was identified as 6,7-dibenzoyl-1,3,5-triphenylcyclopenta[*c*]pyran **39**. Because of the very low yield and to elucidate the structure, the authors designed an alternative synthesis (Scheme 6). The C-alkylation of the potassium salt of

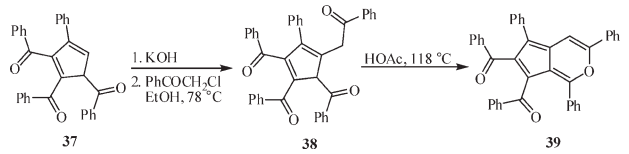
Scheme 4



Scheme 5



Scheme 6



tribenzoylphenylcyclopentadiene **37** with phenacyl chloride, followed by the acid-catalyzed cyclization of **38,** afforded **39** in 18% yield.

In a later work [44], dealing with base-catalyzed rearrangements involving ylide intermediates, **39** was reported as one of the thermolysis products of anhydro-[decyldimethyl(phenacyl)ammonium hydroxide].

Three derivatives of **39** were identified as by-products of analogous reactions [43]. Thus, the thermal decomposition of 4-bromophenacyltrimethylammonium hydroxide in the presence of silver oxide gave the penta-*p*-brominated derivative **40** (Chart 8) as a purple-red solid, while reaction of 4-bromophenacyl chloride with the potassium salt of 1,2,3-tribenzoyl-4-phenylcyclopentadiene afforded the monobromo derivative **41** (Chart 8) as a bright-red solid. The mechanism of formation of cyclopenta[*c*]pyran **40** involves a sequence of reactions starting with the nucleophilic attack of the ammonium ylid *p*-Br—Ph—CO—$^{-}$CH—$^{+}$NMe$_3$ to 4-bromophenacyltrimethylammonium hydroxide followed by the Hofmann elimination of the obtained quaternary ammonium hydroxide and the formation of 1,2-dibenzoylethylene as intermediate. Two successive Michael addition of the ammonium ylid to 1,2-dibenzoylethylene followed by intramolecular cyclizations with the loss of trimethylamine and water gives the cyclopenta[*c*]pyran. This mechanism was also confirmed by the thermal decomposition of 4-bromophenacyltrimethylammonium hydroxide in the presence of *trans*-1,2-dibenzoylethylene which led to another monobromo derivative, that is, **42** (Chart 8) as a dark-red solid.

With their electron-withdrawing effect, the benzoyl or bromobenzoyl groups of **39**–**42** improve the stability of these compounds. It is worth to note that in the natural cyclopenta[*c*]pyrans at least one strong electron-withdrawing substituent is present as well. Although providing only rather small to fair yields, some synthetic strategies were elaborated during the last two decades, which afford cyclopenta[*c*]pyrans without electron-withdrawing substituents. The parent compound **1** and its 6-*tert*-butyl derivative were obtained by Seitz *et al.* [41] using substituted cyclopentadienes as building block. Encouraged by the success with the synthesis of 6-*tert*-butylcyclopenta[*c*]pyran from *tert*-butylcyclopentadiene, the authors applied a similar approach for the preparation of **1** (Scheme 7). Deprotonation of (trimethylsilyl)cyclopentadiene **43** and treatment of the resulting anion **44** with bromoacetaldehyde dimethyl acetal afforded a mixture of tautomers in 55% yield, with **45** as the major component. Its conversion into (dimethylamino)fulvene **46** by heating with *N*,*N*-dimethylformamide dimethyl acetal was described to proceed with a good yield (86%), whereas the hydrolysis of **46**, carried out in two steps, was reported to give **1** in only 5% yield.

In an attempt to improve the yield of the last step of this sequence, it was discovered that the reaction of **45** led not only to the formation of **46** but to that of its regioisomers **47** and **48** as well (Scheme 7) [3], which cannot be converted into **1**. This seems to be the reason for the low yield of **1** reported [41]. The authors of the reinvestigation [3] assumed that the intended steric

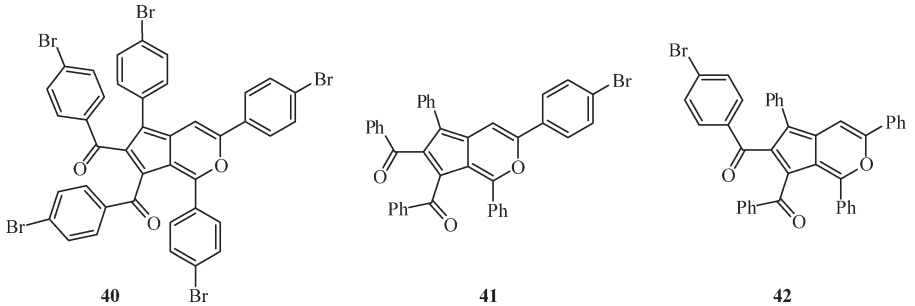
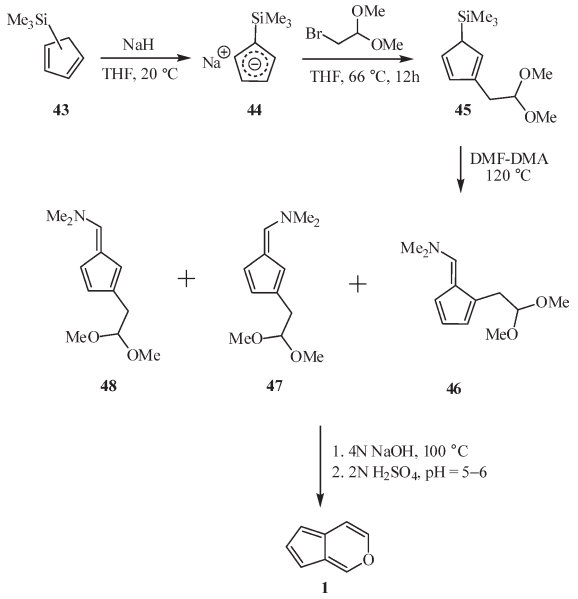


Chart 8

Scheme 7

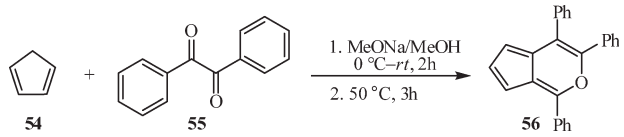


effect of the trimethylsilyl group to direct the (dimethylamino)methylene group next to acetaldehyde acetal side-chain is of no avail, because the protodesilylation of **45** is effectively competing with the desired aminomethylenation already at an early stage of the reaction.

An unexpected route to the cyclopenta[*c*]pyran system was discovered by Kato *et al.* [42,45] in the cycloaddition of the triphenyloxazolium-4-olate **50** with the 2-*ter*t-butyl-6-dimethylaminofulvenes **51**. The bulky substituent of **51** prevented the [4+2] cycloaddition and thus favored the [4+6] cycloaddition. The mesoionic compound **50** was generated *in situ* from *N*-benzoylphenylglyoxyanilide **49** with triethyl phosphite and treated with **51** to give the [4+6] cycloadduct **52**. Under the reaction conditions, **52** suffered spontaneous eliminations of phenylisocyanate and dimethylamine, furnishing the red colored 6-*tert*-butyl-1,3-diphenylcyclopenta[*c*]-pyran **53**, which was isolated in 18% yield (Scheme 8).

A simple one-pot synthesis was reported for 1,3,4-triphenylcyclopenta[*c*]pyran **56**, which was unexpectedly formed during an attempt to prepare fulvenes from α-dicarbonyl compounds [46,47]. The reaction of cyclopentadiene **54** with sodium methoxide in the presence of benzil **55** proceeded in a sequence of condensation, addition and elimination reactions and gave rise to the red solid of **56** in 10% yield (Scheme 9) along with large amounts of methyl benzoate and polymeric material.

Scheme 9

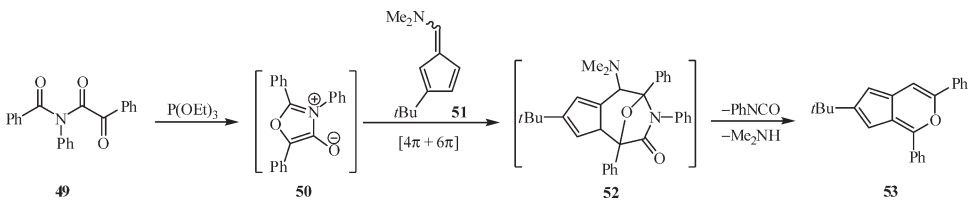


A major breakthrough occurred in 1998, when a general method for the synthesis of 1,4-disubstituted cyclopenta[*c*]pyrans was reported by Christl *et al.* [4]. The three-step sequence starts with a Diels-Alder reaction with inverse electron demand of cyclopentadiene with 6*H*-1,3,4-oxadiazin-6-ones **57** (Scheme 10). This acid-catalyzed cycloaddition led to the formation of the regioisomeric dihydro-α-pyrones **58** and **59** in good yields (69–85%). Next, the conversion of **58** and **59** into the α-pyrones **60** and **61** was achieved by dehydrogenation with DDQ in yields of 27 to 76%. The last step was the reduction of **60** and **61** with DIBAL-H affording the 1,4-disubstituted-cyclopenta[*c*]pyrans **62** in yields ranging from 28 to 53%. An exception was reported for the case of **62c**, obtained in only 9% yield, which is due to the attack of the reagent at the ester group. Consequently, the concomitant reduction of the carbonyl and the ester groups with 4 equiv. of DIBAL-H furnished the primary alcohol corresponding to **62c** in 36% yield. By using $AlMe_3$ instead of DIBAL-H, the isomeric α-pyrones **60a/61a** were converted into the 3-methyl-1,4-diphenylcyclopenta[*c*]pyran in 50% yield.

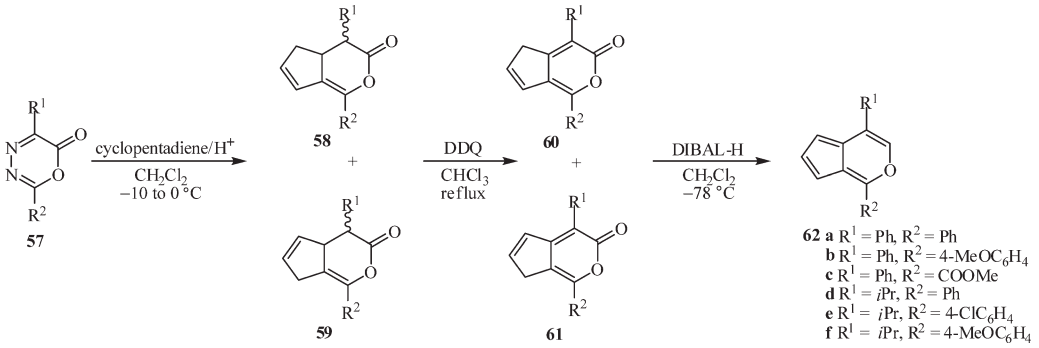
A few years later, the synthesis of a number of 3-substituted cyclopenta[*c*]pyrans was reported by Christl *et al.* [3]. In this project, the authors initially had in mind a more advantageous pathway to the parent cyclopenta[*c*]-pyran **1**, to study its reactivity. Although this attempt failed, the α-pyrones **68a** and **68b** (Scheme 11), originally considered as suitable precursors of **1**, since they are the parent compounds to **60** and **61**, proved to be useful starting materials for the synthesis of the 3-substituted cyclopenta[*c*]pyrans **69–72** and **74–76** (Scheme 12).

On the basis of a known synthesis of the dihydro derivative **66** [48] of **68a** and **68b,** the latter were prepared in six steps from cyclopentanone **63** (Scheme 11), which was converted into the enol ether **64** by a Claisen

Scheme 8



Scheme 10



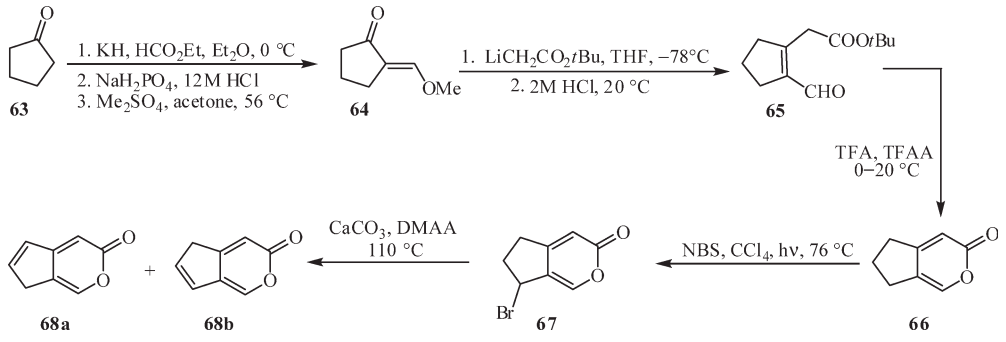
condensation with ethyl formate followed by the methylation of the intermediary enol. The reaction of **64** with the lithium enolate of *tert*-butyl acetate afforded *tert*-butyl (2-formylcyclopent-1-en-1-yl)acetate **65** in 52% yield after chromatographic purification. Next, the cyclization reaction was performed with trifluoroacetic acid (TFA) in trifluoroacetic acid anhydride (TFAA), resulting in the α-pyrone **66** in 76% yield. The best way to get to the α-pyrones **68** was the bromination of **66** with *N*-bromosuccinimide (NBS) followed by the elimination of hydrogen bromide from the resulting bromo-α-pyrone **67** by calcium carbonate in dimethylacetamide (DMAA). The α-pyrones **68a** and **68b** were isolated in yields of 53% and 12%, respectively. Since only **68b** can directly emerge from **67**, **68a** is the result of the base catalyzed isomerization of **68b**. Thus, the final product ratio indicates the greater thermodynamic stability of **68a**.

During several attempts to convert α-pyrones **68a** and **68b** into the cyclopenta[*c*]pyran **1**, the high acidity of the methylene group of **68a** was observed and then demonstrated by deuteration with triethylamine in the presence of D_2O, which gave rise to [5,7,7-D_3]-**68a** and [4,5,7,7-D_4]-**68a** in a ratio of 2:3, indicating a complete H/D exchange in the 5- and 7-positions and, surprisingly, a significant one in the 4-position as well. Based on this result, a number of cyclopenta[*c*]pyrans with an oxygen functionality in 3-position were prepared (Scheme 12), but characterized by ^1H and ^{13}C NMR spectroscopy only due to their high sensitivity toward conversion into **68a** and **68b** even at room temperature.

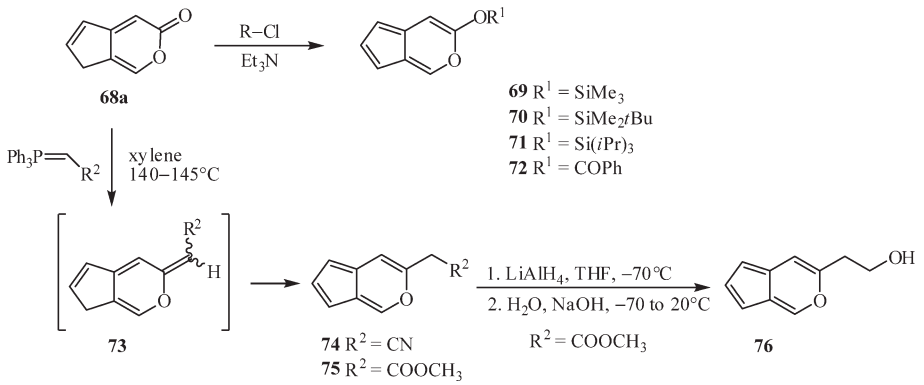
The treatment of **68a** with triethylamine in the presence of different chlorotrialkylsilanes led to ketene acetal **69** and only to a small quantity of **71** (Scheme 12). Considerable improvements were achieved by using the lithium enolate of **68a**, which was obtained from **68a** by the action of either methyllithium or lithium diisopropylamide. Its treatment with *tert*-butylchlorodimethylsilane and chlorotriisopropylsilane at −78°C furnished **70** and **71**, respectively, in significant amounts, while no reactions were observed with diethyl chlorophosphate, diphenyl chlorophosphate or *N,N*-bis(trifluoromethylsulfonyl)aniline. The enol ester **72** was obtained by treatment of **68a** with triethylamine and benzoyl chloride in 65% yield, but several analogous experiments with acyl and sulfonyl chlorides failed [3].

By using the procedures for the olefination of lactones, two 3-substituted cyclopenta[*c*]pyrans were prepared [3]. Thus, the reaction of **68a** with the respective ylides led to the acetonitrile **74** and the methyl acetate **75** (Scheme 12) in yields of 29 and 15%, respectively. The expected intermediates **73** could not be observed, which is why the authors assumed that **73** underwent tautomerism catalyzed by the ylide, which acted as a

Scheme 11



Scheme 12



base and gave rise to the more stable aromatics **74** or **75**. The reduction of **75** by $LiAlH_4$ at low temperatures afforded the primary alcohol **76** (Scheme 12), which could not be purified due to decomposition. On performing this reaction at room temperature, the ring system was attacked as well.

3.3. Fused cyclopenta[*c*]pyrans. In the last decade, the syntheses of some chromene type derivatives of cyclopenta[*c*]pyran were published, which are described below. In addition, a natural product from certain mushrooms (retipolide A **94**) is reviewed, which was transformed to cyclopenta[*c*]pyran derivatives with a 3,4-anullated butyrolactone subunit.

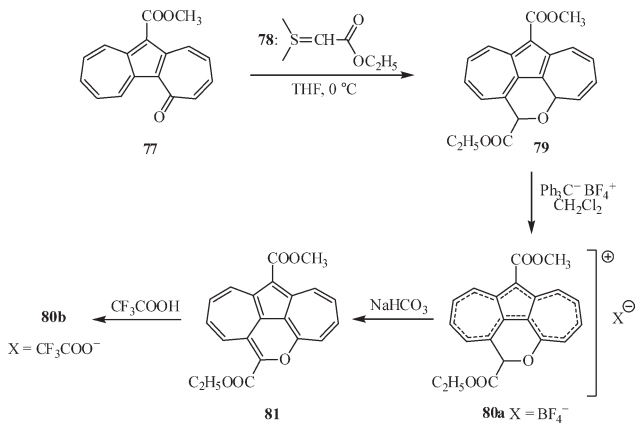
By investigating the reaction of 11-methoxy-5*H*-cyclohepta[*a*]azulen-5-one **77** with ethyl (dimethylsulfuranylidene) acetate (EDSA) **78** [49], the unexpected formation of the heterocyclic compound **79** (Scheme 13) as a sole product (98%) was observed. The hydride abstraction of **79** with trityl tetrafluoroborate quantitatively afforded the cation **80a**, which could be isolated as a reddish brown solid. The derivative **81**, possessing a cyclopenta[*c*]pyran core, was obtained in 24% yield by treatment of cation **80a** with sodium hydrogen carbonate. Another way to achieve **81** was the reaction of **79** with DDQ followed by neutralization with $NaHCO_3$ (65% overall yield). The protonation of **81** with TFA led to the cation **80b**, its structure being confirmed by ^{1}H-NMR spectrum.

By a palladium-copper catalyzed Sonogashira-Hagihara coupling of a diethynylbenzene **82** with 2 equiv. of the iodotrimethylsilylhydroquinone **83**, followed by a tandem intramolecular bicyclization between two alkyne groups and a hydroxy functionality and, finally, the desilylation with potassium fluoride, the indenopyrans **84** (Scheme 14) were obtained [50]. Simultaneously being chromene derivatives, these compounds were characterized by advanced NMR investigations and, in case of **84a**, the molecular structure was also determined by X-ray diffraction.

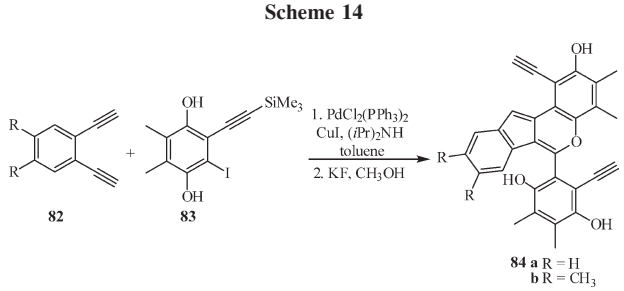
Fulvenes proved to be very useful substrates for the synthesis of a number of cyclopenta[*c*]chromenes **87** (Scheme 15) [51,52]. The hetero [6+3] cycloaddition of aminofulvenes **85** with benzoquinones **86** afforded the products **87** in good yields ranging from 65 to 86%.

A new approach with this method by using the solid-phase synthesis [52] was applied for eleven benzoquinones leading to the target products in good yields and purities higher than 95%. Also, by using indoanilines instead of benzoquinones the corresponding cyclopenta[*c*]quinoline derivatives were obtained. By applying a polystyrene amino resin as solid phase, a 110-

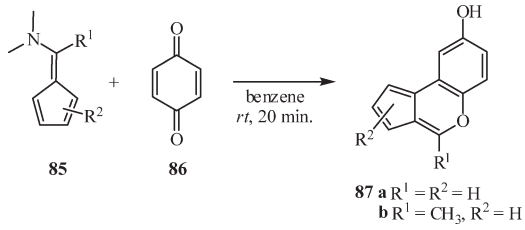
Scheme 13



Scheme 14

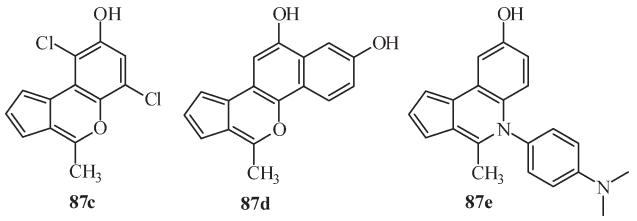


Scheme 15



85 **86**

87 a $R^1 = R^2 = H$
b $R^1 = CH_3$, $R^2 = H$



87c **87d** **87e**

Chart 9

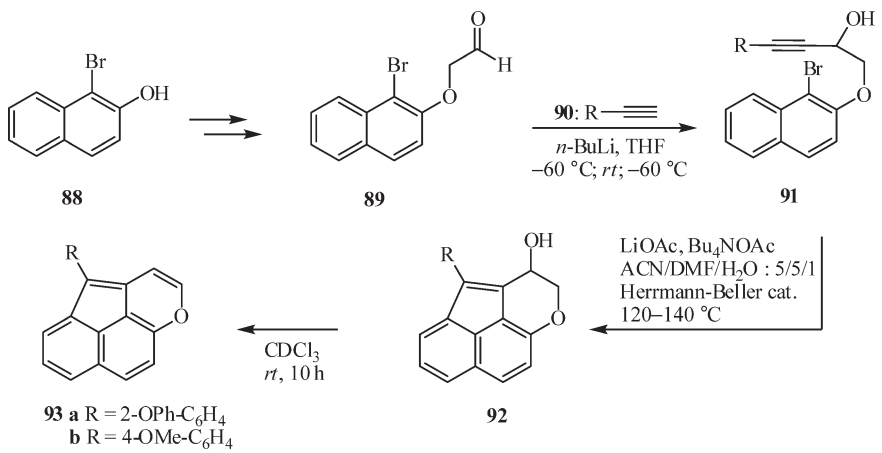
membered heterosteroid library was generated in four steps. The three arbitrary selected products **87c–e** (Chart 9)**,** were obtained in high purity and in overall yields of 38–42%. Preliminary *in vitro* assays revealed a moderate activity against a variety of NCI cancer cell lines for compounds **87c** and **87e** with an average of $GI_{50} = 2.4 \times 10^{-5}$ and 9.5×10^{-6} M, respectively.

The palladium-catalyzed intramolecular cyclisation of a 1-bromonaphthalene, having a side chain in 2-position with an alkyne moiety, allows a highly efficient and regioselective synthesis of the acenaphtylenes **92** (Scheme 16) in domino reactions [53]. The addition of an excess of lithiated alkynes **90** to the (bromonaphthyloxy)acetaldehyde **89**, which was prepared from 1-bromo-2-naphthol **88**, afforded the alcohols **91** in yields over 84%. The domino reactions of **91** were performed by using catalytic amounts of the Herrmann-Beller palladacycle and led to the desired acenaphtylenes **92** in very good yields (74–98%), if the substituent R is an aryl group. By standing in $CDCl_3$ at room temperature for 10 h, the acenaphtylenes **92** underwent a dehydration with formation of **93**, which are heterocycles with 16 π-electrons.

The investigation of mushrooms of genus *Retiboletus retipes*/*ornatipes* revealed the presence of several spiromacrolides, *e.g.,* retipolide A **94** (Scheme 17) [54], which include hydrocyclopenta[*c*]pyran systems. To elucidate the structure of these fungal metabolites and to establish the absolute configuration, the authors carried out some chemical transformations. Thus, **94** was converted into a red, stable product by heating with 2,2-dimethoxypropane and *p*-toluenesulfonic acid (PTSA) in toluene. As revealed by the pattern of the signals in the ^{1}H-NMR spectrum, the compound contained a cyclopenta[*c*]pyran unit and was assigned structure **95a.** This result contributed to the elucidation of the constitution of retipolide A **94**. The absolute configuration of **94** was determined by its conversion into the derivative **95b** by heating with 2,2-bis[(*S*)-*sec*-butoxy]propane in toluene. The molecular structure of **95b**, as determined by single crystal X-ray diffraction, confirmed the conformation deduced from the NMR spectroscopic parameters in solution. By means of the *S* configuration of the *sec*-butyl ether group introduced, the absolute configuration of the spiro carbon atom could be determined to be *R*. Since the conversion of **94** into **95b** does not affect the spiro carbon atom, one may conclude that this carbon atom of **94** possesses also the *R* configuration.

The treatment of **94** with acetic anhydride in the presence of concentrated sulfuric acid as catalyst led to a mixture of acetylation products, from which the diacetate **96a** and triacetyl derivative **96b** were isolated and analyzed (Scheme 17).

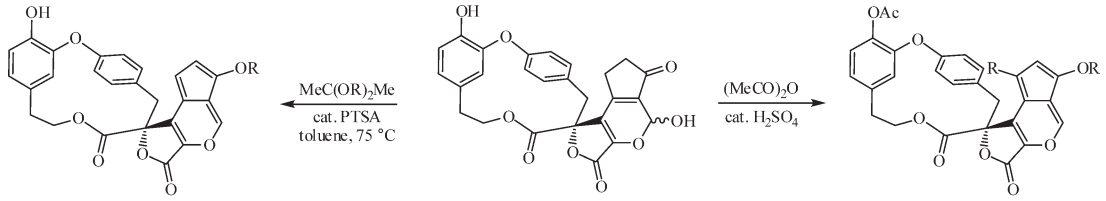
Scheme 16



88 **89** **91** **92**

93 a R = 2-OPh-C_6H_4
b R = 4-OMe-C_6H_4

Scheme 17



95 a R = Me
b R = (*S*)-*sec*-Bu

94
Retipolide A

96 a R = H
b R = Ac

4. STRUCTURAL ANALYSIS AND PROPERTIES

Generally, pseudoazulenes are rather sensitive compounds in comparison with azulene. In the series of pseudoazulenes, the stability decreases dramatically on going from the nitrogen- and sulphur-containing systems to the oxygen analogues [1,55].

The unsubstituted cyclopenta[*c*]pyran **1** (Chart 1) could not be obtained free of diisopropyl ether, utilized as solvent in the preparation, due to its volatility and thermal instability [41]. Low stability, in particular sensitivity to acids, demands purification under special conditions, that is, basic alumina as stationary phase on chromatography. The sensitivity of derivatives of **1** is influenced by the number and the nature of the substituents. Thus, 6-*tert*-butylcyclopenta[*c*]pyran could be isolated as a lemon-yellow solid and kept for several months at 4°C. A comparison of the 1,4-disubstituted cyclopenta[*c*]pyrans showed a higher stability of the diaryl derivatives **62a–c** than that of the isopropylaryl derivatives **62d–f**, probably because the former could be isolated as crystals and the latter only as oils [4].

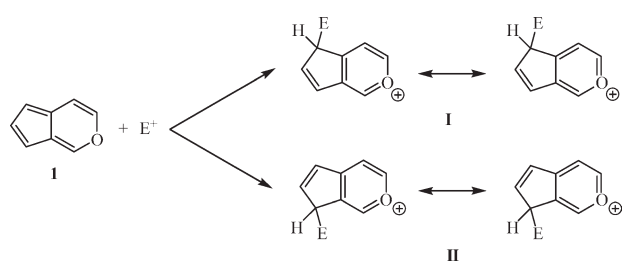
Expectedly, an increased stability is observed for derivatives with at least one electron-withdrawing substituent in conjugation with the π-electrons of the ring system. The best illustration of this effect is provided by natural products with an electron-withdrawing substituent at position 7 such as a formyl group in most cases and a carboxyl or an ester group in others (see section 2).

Quantum chemical calculations offered important data related to aromaticity and reactivity of pseudoazulenes [1]. The results show that the aromatic character of the nitrogen derivatives is stronger than that of the oxygen analogues. For all pseudoazulenes, an electron deficiency in the six-membered ring and an electron surplus in the five-membered ring were calculated. As in case of azulenes, electrophilic substitutions in pseudoazulenes take place in the five-membered ring at positions 5 and 7, as illustated by the mesomeric structures of the intermediates **I** and **II** after attack of an electrophile E^+ at cyclopenta[*c*]pyran **1** (Scheme 18). Molecular orbital calculations predict the highest electron density at position 7 for the pseudoazulene-[*c*]-series. The calculation of this quantity of cerbinal **12** [56] as well as cyclopenta[*c*]pyrans **1** and **56** [47] resulted in similar values at positions 5 and 7.

Although a considerable number of electrophilic substitutions are known for pseudoazulenes [1,55], there are only two papers dealing with electrophilic substitutions of cyclopenta[*c*]pyrans [3,4]. They were carried out with compounds **62a–f** and **74–76** and had to be performed in nonacidic media [3,4]. The presence of any acid had to be avoided, since otherwise protonation would have predominated. The high selectivity for an attack of an electrophile at position 7 was suggested by calculations and experimentally confirmed by the formation of the pyrylium salts **97** on treatment of compound **56** with TFA (Scheme 19) [47]. By action of perchloric acid in acetic acid on fulvoipolamiide **20** (Chart 7), the red-orange color of **20** was replaced by a blue one, which is characteristic for pyrylium salts. This color change is caused by the bathochromic shift of the longest wavelength absorption from 435 to 630 nm [32].

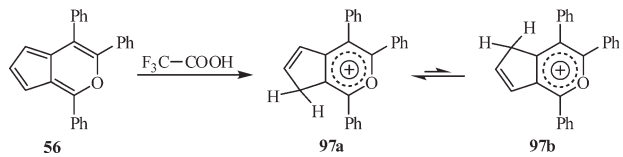
As reported in the cases of compounds **62a–f** and **74–76** and depicted in Scheme 20 [3,4], electrophilic monosubstitution can easily be achieved. Important to note is the Vilsmeier-Haack formylation of 1,4-disubstituted cyclopenta[*c*]pyrans and of 1,3,4-trisubstituted one **98** with DMF/$POCl_3$ at 0°C, giving rise to the corresponding

Scheme 18



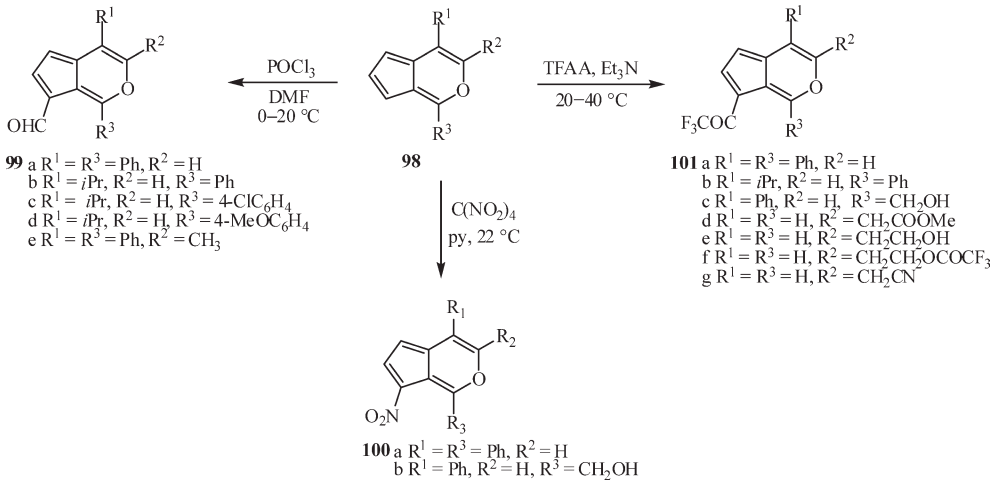
1 **I** **II**

Scheme 19



56 **97a** **97b**

Scheme 20



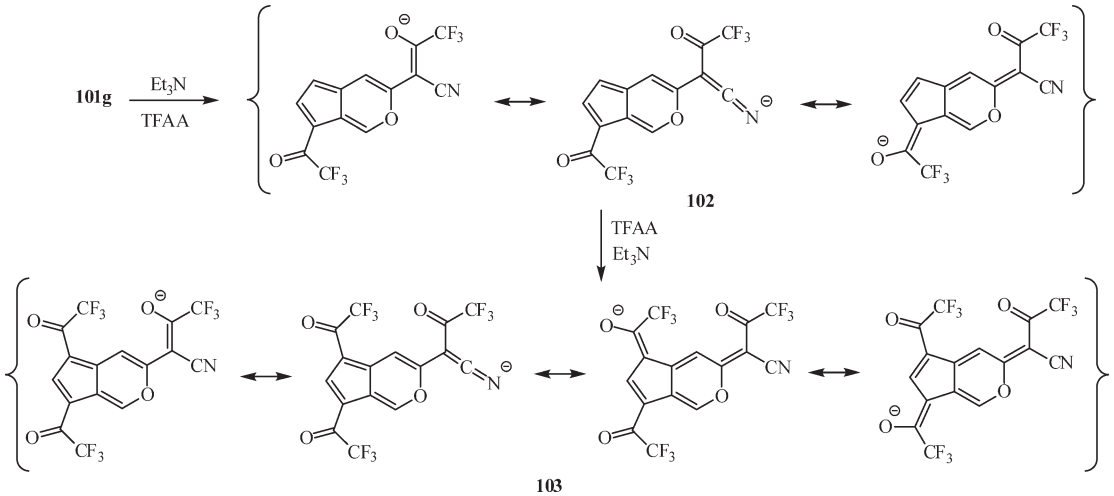
cyclopenta[*c*]pyran-7-carbaldehydes **99a–e** in yields of 61 to 84%. These compounds are related to the natural products **9**–**19**, most of which carry a formyl group at C-7 as well. The nitroderivatives **100a** and **100b** were prepared in yields of 56 and 38%, respectively, by reaction of the respective substrates **98** with tetranitromethane in pyridine at 0 °C. A notable number of trifluoroacetylated compounds were obtained from reaction of **98** with TFAA in the presence of triethylamine (Et_3N). It is worthy to note that trifluoroacetylation was the only substitution reaction that worked in the case of 3-substituted cyclopenta[*c*]pyrans **98**, giving rise to the products **101d–g** in yields ranging from 11 to 42% [3]. The introduction of the above electron-withdrawing groups reduces the reactivity of the cyclopenta[*c*]pyran system and thus enhances its stability.

Addition of TFAA/Et_3N in excess to acetonitriles **74** or **101g** (Scheme 21) led to products with two and three trifluoroacetyl groups, which are salts consisting of highly resonance-stabilized anions **102** and **103,** respectively, and triethylammonium ions [3].

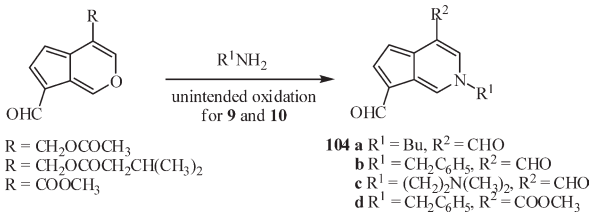
Cyclopenta[*c*]pyrans were used as starting materials for the synthesis of their nitrogen analogues, that is, cyclopenta[*c*]pyridines [8,57]. The conversion of baldrinal **9** and homobaldrinal **10** into the cyclopenta[*c*]pyridines **104a–c** by treatment with primary amines (Scheme 22) proceeded in low to fair yields (11–29%), which was explained by the simultaneous, but unintended oxidation of the side chain at C-4 [57]. The reactions of mixtures of **9** and **10** with the biogenic amines tyramine and histamine gave the corresponding cyclopenta[*c*]pyridines, but their yields and purities were rather unsatisfactory. However, the O/N exchange occurred very quickly on treatment of cerbinal **12** with excess of benzylamine in THF at *rt* and gave rise to the cyclopenta[*c*]pyridine derivative **104d** (Scheme 22) [8].

The hydrogenation of the cyclopenta[*c*]pyran unit can be easily achieved. Such a reaction was performed with

Scheme 21



Scheme 22



9 R = CH_2OCOCH_3
10 R = $CH_2OCOCH_2CH(CH_3)_2$
12 R = $COOCH_3$

104 a R^1 = Bu, R^2 = CHO
b R^1 = $CH_2C_6H_5$, R^2 = CHO
c R^1 = $(CH_2)_2N(CH_3)_2$, R^2 = CHO
d R^1 = $CH_2C_6H_5$, R^2 = $COOCH_3$

the benzocyclopenta[*c*]chromene **87a**, which possesses the basic skeleton of the 11-oxasteroids [51]. The catalytic hydrogenation of **87a** with a Pd-C catalyst afforded the hexahydro and decahydro derivatives **105** and **106** of **87a** in yields of 85 and 82%, respectively (Scheme 23).

Although quantum chemical calculations predicted for the [*c*]-series of pseudoazulnes position C-1 as being susceptible for a nucleophilic or a radical attack [1], there are no such reactions reported in the literature for the cyclopenta[*c*]pyran system.

Cyclopenta[*c*]pyrans are colored compounds. The parent compound **1** (Chart 1) has a lemon-yellow color in solution, and generally, both, naturally occurring and non-natural cyclopenta[*c*]pyrans were isolated as yellow to intense red solids or oils. Consequently, in the UV-vis spectra, the absorption maxima at longest wavelengths were found to vary between 367 and 493 nm [3,4,11,16,20,26,29,31,32,34,41–43,47]. Although there are no systematic investigations as to the influence of substituents on the position of the longest wavelength absorption, one may observe that the presence of an electron-withdrawing substituent results in a bathochromic shift, though it may be very small, and also in an increase of the molecular extinction coefficient. For example, the introduction of a trifluoroacetyl group on cyclopenta[*c*]pyrans **98** (Scheme 20) causes an increase of the molecular extinction coefficient to the six- and nine-fold value and a bathochromic shift of 34 and 38 nm for compounds **101g** and **101d**, respectively [3]. Moreover, the highly resonance-stabilized anion **103** (Scheme 21) absorbs at λ_{max} (log ε) = 490 nm (4.27) and is the first member of a new class of strongly fluorescing compounds with a fluorescence quantum yield $\Phi_f = 0.55$ on excitation at 450 nm [3].

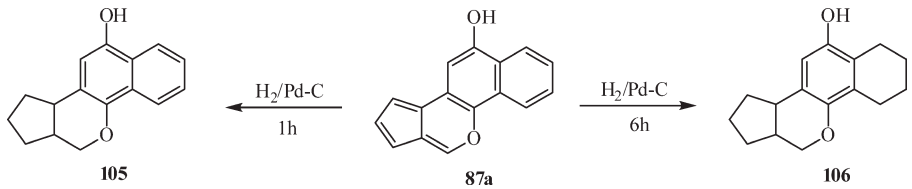
The structural characterization by NMR spectroscopy was reported for nearly all cyclopenta[*c*]pyrans mentioned here. Chemical shifts are in the typical region for heteroaromatic compounds, as illustrated by the six signals in the range of 6.39 to 8.72 ppm recorded for the parent cyclopenta[*c*]pyran **1** [41]. An interesting correlation with the aromaticity of the cyclopenta[*c*]pyran system was found in the values of the coupling constants. As revealed by the ^{1}H NMR spectrum of **1** [41], the vicinal coupling constants in the five-membered ring have different values (Chart 10) and thus indicate an uneven electron density distribution at C-5, C-6 and C-7, which is in accordance with quantum chemical calculations for pseudoazulenes [1]. Seitz *et al.* [41] compared $J_{6,7}$ and $J_{5,6}$ of cyclopenta[*c*]pyran **1** with those of the cyclopenta[*c*]thiapyran derivative **107** and the cyclopenta[*c*]pyridine derivative **108** (Chart 10). The largest difference between the two values (ΔJ) resulted for **1** and the smallest one for **108**. A smaller value of ΔJ indicates a more pronounced aromatic character of the compound. Hence, **1** is clearly less aromatic than **108**, which, once again, is in accord with quantum chemical calculations [1].

	$J_{6,7}$ (Hz)	$J_{5,6}$ (Hz)	ΔJ
1	4.6	2.3	**2.3**
107	4.4	3.1	**1.3**
108	4.1	3.3	**0.8**

Chart 10

Important information on the structure of cyclopenta[*c*]pyrans in the solid state is provided by single crystal X-ray diffraction. Heretofore, eight compounds [4,33,34,46,50,54,56] were investigated by this method. Three of them are of natural origin, namely cerbinal **12** [56], fulvoipolamiide **20** [33] and torricellate **21** [34]. Most of these cyclopenta[*c*]pyrans crystallize in monoclinic or orthorhombic crystal systems, whereas a triclinic space group was found for compound **56** [46]. X-ray structure analysis confirmed the planar structure of cyclopenta[*c*]pyrans, which was also suggested by NMR spectra and theoretical calculations. Cerbinal **12**

Scheme 23



105 **87a** **106**

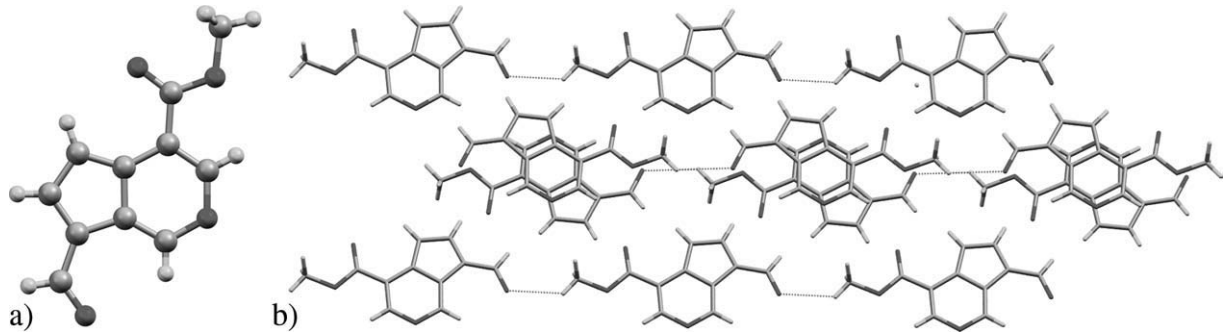


Figure 1. (a) Molecular structure of cerbinal **12** and (b) view of the lattice of **12** (Mercury representation).

exhibits a highly conjugated π-system having the ester and formyl groups coplanar with the cyclopenta[*c*]pyran unit (Fig. 1) [56]. The weak intra- and intermolecular C—H···O interactions and intermolecular π stacking influence the packing structure of the crystal of **12** (Fig. 1) and provide its stability.

Interestingly, the C—C bond length in the five-membered ring of compounds **62b** and **99b** (Fig. 2) are nearly the same and similar to those of benzene and the corresponding ones of azulenes [4]. The formyl group of **99b** is almost coplanar with the five-membered ring but causes remarkable changes in bond lengths of the pyran subunit. The aryl groups of compounds **56**, **62b,** and **99b** deviate from the plane of cyclopenta[*c*]pyran core and, in case of **56**, the three phenyl groups exhibit dihedral angles of 33°, 49°, and 50° [46,47].

5. CONCLUSIONS

This review is the first dealing with a less exploited pseudoazulene class, the cyclopenta[*c*]pyrans. Herein, we have presented up to date methods of synthesis, structural analysis and reactivity. The high sensitivity to acidic or alkaline media makes the synthesis of this 10π aromatic system a continuous challenge. A general procedure could not be elaborated yet, but various strategies starting from cyclopentadienes, fulvenes, oxadiazinones or α-pyrones were developed according to the substitution patterns of the target compounds. Investigations of electrophilic substitutions led to interesting results, and the formation of a fluorescent compound may open a new direction in the chemistry of cyclopenta[*c*]pyrans.

The biological properties of cyclopenta[*c*]pyrans of natural occurrence are of great interest. Several compounds have been extracted from plants, used in traditional medicine, and investigated for phytotherapeutic, cytotoxic, sedative, antifungal, antiviral, antimicrobial, or antitumor activities. Strategies utilizing total or partial synthesis have been developed for some of these natural compounds.

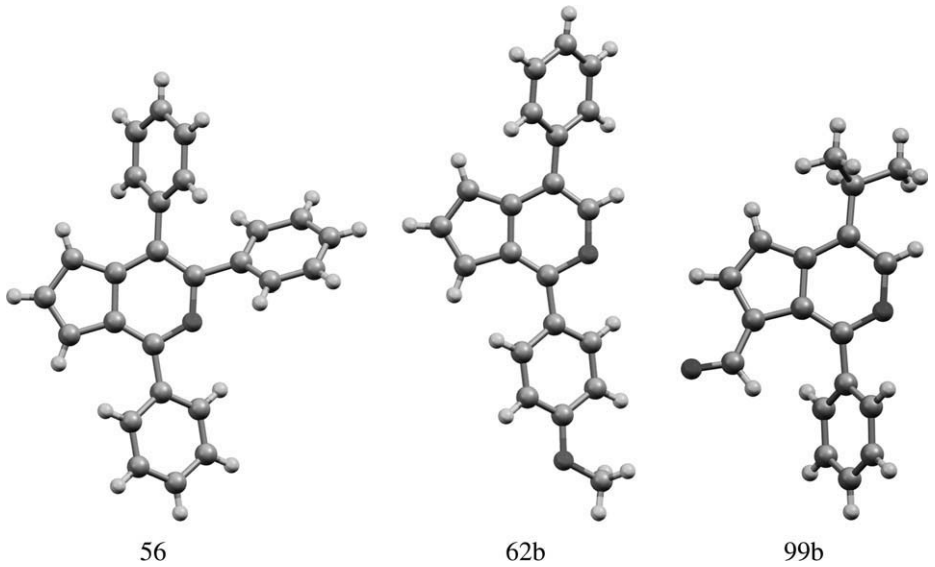


Figure 2. Molecular structures of compounds **56**, **62b,** and **99b** (Mercury representations).

Acknowledgments. We are grateful to Prof. Manfred Christl for the valuable discussions during the preparation of the manuscript. This work was supported by CNCSIS-UEFISCSU, PN II program, grants ID_2278, TD_108, and ANCS grant 128 CP/I. E. B. thanks the Alexander von Humboldt Foundation and the Hertie Foundation for a return fellowship.

REFERENCES AND NOTES

[1] Timpe, H.-J.; El'tsov, A. V. Adv Heterocycl Chem 1983, 33, 185.

[2] Mayer, R.; Weise, U. Naturwissenschaften 1958, 45, 312.

[3] Güllük, E.; Bogdan, E.; Christl, M. Eur J Org Chem 2006, 531.

[4] Christl, M.; Bien, N.; Bodenschatz, G.; Feineis, E.; Hegmann, J.; Hofmann, C.; Mertelmeyer, S.; Ostheimer, J.; Sammtleben, F.; Wehner, S.; Peters, E.-M.; Peters, K.; Pfeiffer, M.; Stalke, D. Chem Commun 1998, 2387.

[5] Nangia, A.; Prasuna, G.; Rao, P. B. Tetrahedron 1997, 53, 14507.

[6] Pavan, M. Ric Sci 1949, 19, 1011.

[7] Dinda, B.; Debnath, S.; Harigaya, Y. Chem Pharm Bull 2007, 55, 159.

[8] Isoe, S. Stud Nat Prod Chem 1995, 16, 289.

[9] Nakanishi, K. Natural Products Chemistry; Kodansha Scientific Ltd.: Tokyo; Academic Press: New York, 1974; Vol. 1, pp 48.

[10] Thies, P. W. Tetrahedron 1968, 24, 313.

[11] Chen, Y.-G.; Yu, L.-L.; Huang, R.; Lv, Y.-P.; Gui S.-H. Arch Pharmacal Res 2005, 28, 1161.

[12] Chang, V.; Boon H. Herb & Supplements: Valerian, 2008. Available at: http://camline.ca/professionalreview/pr_print.php?NHPID=72.

[13] Bos, R.; Woerdenbag, H. J.; Van Putten, F.; Hendriks, H.; Scheffer, J. J. C. Phytochem Anal 1996, 7, 143.

[14] Bos, R.; Hendriks, H.; Scheffer, J. J. C.; Woerdenbag, H. J. Phytomedicine 1998, 5, 219.

[15] Schneider, G.; Willem, M. Arch Pharm 1982, 315, 691.

[16] Schneider, G.; Willem, M. Arch Pharm 1979, 312, 555.

[17] Mersch-Sundermann, V.; Schneider, U.; Klopman, G.; Rosenkranz, H. S. Mutagenesis 1994, 9, 205.

[18] Hassan, E.; Tayebeh, R.; Samaneh, E. T.; Vahid, N.; Vali-O-Allah, M. J Biol Sci (Faisalabad, Pak.) 2008, 8, 549.

[19] Hassan, E.; Tayebeh, R.; Samaneh, E. T.; Zeinalabedin, B. S.; Vahid, N.; Mehdi, Z. Asian J Plant Sci 2008, 7, 195.

[20] Fumiko, A.; Hikaru, O.; Tatsuo, Y. Chem Pharm Bull 1977, 25, 3422.

[21] Ohashi, H.; Tsurushima, T.; Ueno, T.; Fukami, H. Agric Biol Chem 1986, 50, 2655.

[22] Godeau, R.-P.; Rossi J.-C.; Fouraste, I. Phytochemistry 1977, 16, 604.

[23] Ivanov, V. D.; Komissarenko, N. F.; Ladygina, E. Ya. Chem Nat Prod 1983, 19, 233.

[24] Godeau, R. P.; Pélissier, Y.; Fourasté, I. Trav Soc Pharm Montp 1978, 38, 343.

[25] Joshi, K. C.; Singh, P.; Taneja, S.; Cox, P. J.; Howie, R. A.; Thomson, R. H. Tetrahedron 1982, 38, 2703.

[26] Kuma, U. S.; Tiwari, A. K.; Reddy, S. V.; Aparna, P.; Ali, A. Z.; Rao, R. J. J Nat Prod 2005, 68, 1615.

[27] Harmata, M. Strategies and Tactics in Organic Synthesis; Elsevier: London, 2004; Vol. 5, pp 419.

[28] Jackson, S. J.; Houghton, P. J.; Retsas, S.; Photiou, A. Planta Med 2000, 66, 758.

[29] Koehn, F. E.; Gunasekera, S. P.; Niel, D. N.; Cross, S. S. Tetrahedron Lett 1991, 32, 169.

[30] Shimano, K.; Ge, Y.; Sakaguchi, K.; Isoe, S. Tetrahedron Lett 1996, 37, 2253.

[31] Schneider, G.; Veith, J. Arch Pharm 1985, 318, 515.

[32] Bianco, A.; Guiso, M.; Iavarone, C.; Marini-Bettolo, R.; Trogolo, C. Gazz Chim Ital 1976, 106, 733.

[33] Viccini, L. F.; Silva, P. S.; de Almeida, M. V.; Saraiva, M. F.; Peixoto, P. H. P.; Salimena, F. R. G.; Diniz, R.; Rodrigues, B. L.; Scowen, I.; Edwards, H. G. M.; de Oliveira, L. F. C. J Mol Struct 2008, 875, 27.

[34] Liang, G.; Xu, B.; Pan, W.; Cao, P.; Zhang, Y.; Lu, Y.; Wu, Y.; Hao, X. Nat Prod Res 2009, 23, 1.

[35] Zhang, Y.; He, H.; Di, Y.; Mu, S.; Wang, Y.; Wang, J.; Li, C.; Kong, N.; Gao, S.; Hao, X. Tetrahedron Lett 2007, 48, 9104.

[36] Chaudhuri, R. K.; Ikeda, T.; Hutchinson, C. R. J Am Chem Soc 1984, 106, 6004.

[37] Pal, A.; Bhattacharjya, A. J Org Chem 2001, 66, 9071.

[38] Chavez, D. E.; Jacobsen, E. N. Org Lett 2003, 5, 2563.

[39] Brayer, J. L.; Alazard, J. P.; Thal, C. J Chem Soc Chem Commun 1983, 257.

[40] Ge, Y.; Isoe, S. Chem Lett 1992, 139.

[41] Kämpchen, T.; Moddelmog, G.; Schulz, D.; Seitz, G. Liebigs Ann Chem 1988, 9, 855.

[42] Kato, H.; Kobayashi, T.; Ciobanu, M.; Kakehi, A. Tetrahedron 1997, 53, 9921.

[43] Harley-Mason, J.; Harrison, C. R. J Chem Soc 1963, 4872.

[44] Jemison, R. W.; Mageswaran, S.; Ollis, W. D.; Sutherland, I. O.; Thebtaranonth, Y.; J Chem Soc Perkin 1 1981, 1155.

[45] Kato, H.; Kobayashi, T.; Ciobanu, M.; Iga, H.; Akutsu, A.; Kakehi, A. Chem Commun 1996, 1011.

[46] Banciu, M. D.; Castellano, E. E.; Ellena, J.; Haiduc, I.; Draghici, C.; Balaban, A. T. New J Chem 2001, 25, 1472.

[47] Banciu, M. D.; Balaban, A. T.; Draghici, C.; Haiduc, I.; Ivanciuc, O. Rev Roum Chim 2002, 47, 705.

[48] Dieter, R. K.; Fishpaugh, J. R. J Org Chem 1988, 53, 2031.

[49] Yasunami, M.; Takagi, A.; Takase, K. Chem Lett 1982, 11, 2027.

[50] Chakraborty, M.; McConville, D. B.; Saito, T.; Meng, H.; Rinaldi, P. L.; Tessier, C. A.; Youngs, W. J. Tetrahedron Lett 1998, 39, 8237.

[51] Hong, B.-C.; Sun, H.-I.; Chen, Z.-Y. Chem Commun 1999, 2125.

[52] Hong, B.-C.; Chen, Z.-Y.; Chen, W.-H. Org Lett 2000, 2, 2647.

[53] Tietze, L. F.; Lotz, F. Eur J Org Chem 2006, 20, 4676.

[54] Justus, K.; Herrmann, R.; Klamann, J.-D.; Gruber, G.; Hellwig, V.; Ingerl, A.; Polborn, K.; Steffan, B.; Steglich, W. Eur J Org Chem 2007, 5560.

[55] Porshnev, Y. N.; Churkina, V. A.; Cherkashin, M. I. Russ Chem Rev 1987, 56, 52.

[56] Laphookhieo, S.; Karalai, C.; Chantrapromma, S.; Fun, H. K.; Usman, A.; Rat-a-Pa, Y.; Chantrapromma, K. Acta Crystallogr Sect C 2001, 57, 1352.

[57] Seitz, G.; Moddelmog, G.; Hölzl, J. Arch Pharm 1985, 318, 946.