Russian Chemical Reviews **82** (5) 393 – 411 (2013) © 2013 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2013v082n05ABEH004361

Synthesis of allocolchicinoids: a 50 year journey

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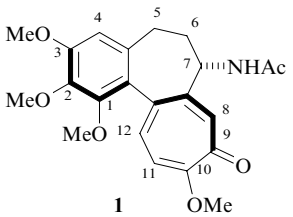
Abstract. Published data on the stereo- and enantioselective synthesis of allocolchicinoids, which are of interest as antitumour agents, are summarized. The stereochemistry of these compounds is described. Two key approaches to their preparation are considered, namely, the synthesis from natural colchicine and total synthesis from commercially available reagents. Various total syntheses of *N*-acetylcolchicinol are performed using biaryl oxidative and reductive coupling, cyclopropanation – ring expansion and Nicholas reaction. The synthetic routes to allocolchicine are based on Diels – Alder cycloaddition, combination of metathesis and Diels – Alder reaction and direct catalytic CH-arylation. Analogues of the colchicine site ligands incorporating heteroaromatic rings are briefly considered; their structural features and methods of synthesis are discussed. The bibliography includes 144 references.

I. Introduction

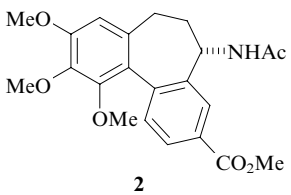
(a*R*,7*S*)-Colchicine [(−)-colchicine, **1**],[1–3] the major alkaloid of meadow saffron (*Colchicum autumnale*), was first isolated in a pure state by Pelletier and Caventou[4] in 1821 but it was not until 1945 that its correct molecular structure was proposed by Dewar.[5] Since the beginning of the 16th century, this compound has been used in minor amounts as an anti-inflammatory agent to treat gout[6] and Mediterranean fever.[7] Enhanced interest in colchicine (**1**) was triggered by the data published by Lits,[8] Dustin[9] and Amoroso[10] that indicated the ability of this alkaloid to inhibit the division of cancer cells in mice and induce tumour regression.

Colchicine is among natural compounds that are most difficult to synthesize. The first total synthesis of colchicine was accomplished by Eschenmoser and co-workers[11] in 1959. They performed 22 steps starting from purpurogallin and obtained the product in 0.00006% overall yield. Subsequently more than a dozen of other synthetic strategies have been proposed; they reflected the development of the art of organic synthesis during the last five decades.[12]

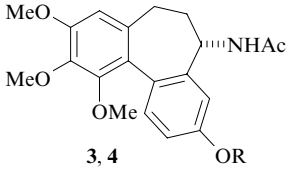
The biological properties of colchicine (**1**) are due first of all to its ability to bind to the intracellular protein tubulin, which forms the microtubules of the spindle in cell division.[13,14] The catalytic domain of the quaternary structure of the protein to which the alkaloid binds has been called the colchicine site of tubulin.[15,16] Being bound to tubulin, colchicine disrupts the formation of the mitotic spindle in the cell; hence, the cell cycle stops in the G2/M phase, and this ultimately results in apoptosis (programmed cell death).[17–19] Since intensive and uncontrolled cell division is the key characteristics of malignant cells, colchicine can efficiently induce apoptosis of tumour cells by inhibiting the mitotic process.



1



2



3, **4**

R = H (**3**), PO(OH)$_2$ (ZD6126, **4**)

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Received 29 November 2012
Uspekhi Khimii **82** (5) 393 – 411 (2013); translated by Z P Svitanko

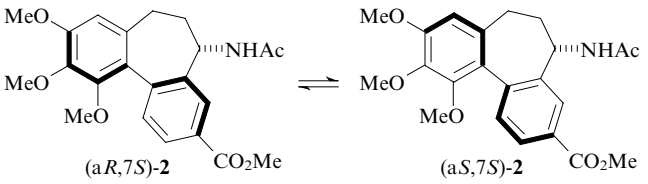
The clinical use of colchicine as an antitumour agent is hampered by its low therapeutic index (high neurotoxicity in effective chemotherapeutic doses).[20–22] Nevertheless, owing to the high antimitotic activity, the molecular structure of colchicine became the reference point in the search for more selective structural analogues. Among them are allocolchicinoids in which the tropolone ring has been replaced by a benzene ring, namely, the natural alkaloid (−)-allocolchicine (**2**)[2] and synthetic (−)-*N*-acetylcolchinol (NAC, **3**);[23,24] the water-soluble form of the latter called ZD6126 (**4**) has reached phase II clinical trials (the trials were terminated due to the revealed cardiotoxicity of therapeutic doses). Nevertheless, owing to the relative simplicity of the molecular structure and high antitumour activities, allocolchicinoids are among the most promising classes of ligands of the colchicine site of the intracellular protein tubulin. The present review surveys the known strategies for the synthesis of allocolchicine derivatives.

II. Stereochemistry of colchicine and allocolchicinoids

Colchicine (**1**) has a unique chemical structure and stereochemistry. Its tricyclic molecular skeleton includes a tropolone ring fused to a cycloheptane ring and has an axis of chirality the configuration of which is determined by the C(7) stereocentre. It should be stressed that the colchicine molecule exists as a single axial (a*R*,7*S*)-isomer,[12] obviously because this isomer is energetically much more favourable than the (a*S*,7*S*)-form (according to density functional theory quantum chemical calculations, the difference between the energies of these conformers[25] was estimated as 3.1 kcal mol^{-1}).

Allocolchicine (**2**) and its derivatives also have an axis of chirality. However, unlike colchicine (**1**), these compounds exist in solution at room temperature as mixtures of axial isomers, which was confirmed by ^{1}H and ^{13}C NMR data (Scheme 1).[26–33] It was shown that the isomer ratio depends on the solvent polarity.[30,33] This may be due to more efficient solvation of the acetamide group located in the pseudoequatorial position and to the fact that the (a*R*,7*S*)-isomer becomes thermodynamically more favourable in solvating solvents.[25]

Scheme 1



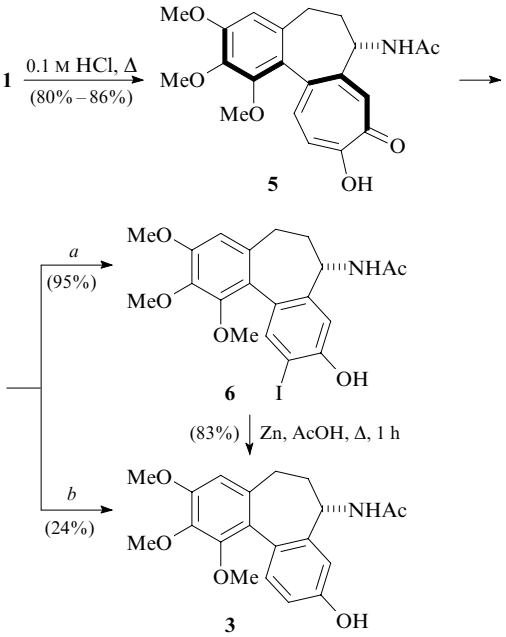
The existence of allocolchicinoids in solution as mixtures of isomers eliminates the need to control the configuration of the chirality axis during the synthesis and reduces the task of a synthetic chemist to correct setting of the stereocentre geometry. However, the conformational lability leaves open the question of which of the two possible conformers (or both?) can bind to tubulin, the intracellular target of allocolchicine antitumour agents. Therefore, attempts were made to obtain configurationally stable allocolchicinoids where interconversion of atropoisomers requires a high energy barrier.[31,32,34–36] The synthesis of these compounds is described in Sections V.1 and V.2.

III. Preparation of allocolchicine derivatives from natural colchicine

Until recently, allocolchicinoids have been mainly prepared by synthetic transformation of colchicine (**1**), which is isolated on a commercial scale (for treating gout) from the lily *Gloriosa Superba*, which grows in northern India. Historically, Windaus' method[37] patented[38] in 2002 is significant due to the commercial interest in *N*-acetylcolchinol (**3**).

According to this method (Scheme 2), (−)-colchiceine (**5**) (Ref. 39) formed upon acid hydrolysis of colchicine (**1**) was converted to *N*-acetyliodocolchinol (**6**) by the reaction with sodium hypoiodite obtained *in situ*. The subsequent reductive dehalogenation with zinc in acidic solution resulted in NAC (**3**), the overall yield over three steps being 63% – 68%. The oxidative contraction of the tropolone ring in colchiceine (**5**) can also be induced by an alkaline solution of hydrogen peroxide on heating (see Scheme 2); however, the yield of the target product is only ~24%.[40]

Scheme 2



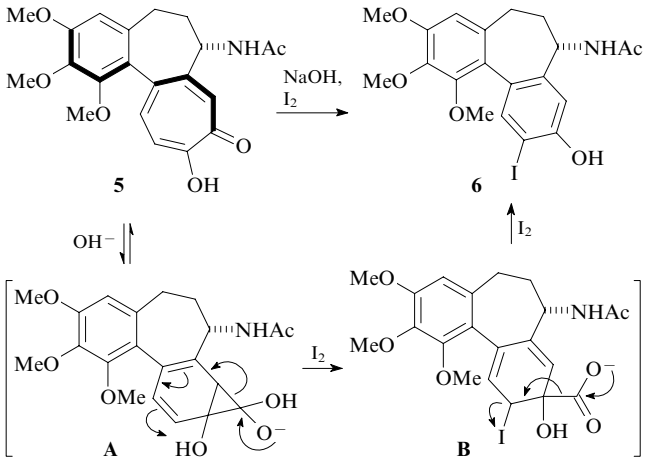
(*a*) NaOH, I_2, NaI, 0 – 5 °C, 1 h;
(*b*) 0.1 M NaOH – 30% H_2O_2 (1 : 1), 60 °C, 2 h

Presumably, the oxidative transformation of colchicine (**5**) to *N*-acetyliodocolchinol (**6**) includes the reversible step of nucleophilic addition of the hydroxide anion to the tropolone carbonyl group followed by disrotatory 6π-electrocyclization to give anion **A** (Scheme 3).[41] The opening of the three-membered ring in this anion followed by iodination and elimination of CO_2 from intermediate **B** furnishes derivative **6** in high yield.[41]

The oxidative degradation of colchicine (**1**) to *N*-acetylcolchinol *O*-methyl ether (NCME, **7**)[42] was accomplished by photooxidation of colchicine (**1**) to endoperoxide **8** in the presence of hematoporphyrin (hmporph) as a photosensitizer and subsequent reductive transformation of compound **8** on treatment with triphenylphosphine (Scheme 4).[43]

One more important aspect of the colchicine chemistry is its base-catalyzed rearrangement to allocolchicine (**2**)[44] and allocolchiceine (**9**);[45] in turn, each of these products can be

Scheme 3



converted to NAC (**3**) (Scheme 5). For example, Fernholz [44] converted acid **9** to arylamine **10** by using the Schmidt reaction.[46, 47] Diazotization of amine **10** followed by hydrolysis gave NAC (**3**) in 33% yield. In 2005, a method for the synthesis of NAC from allocolchicine (**2**) *via* alcohol **11** and hydroperoxide **12** was patented (see Scheme 5).[48] The transformation of compound **12** to NAC (**3**) follows the same mechanism as the preparation of phenol from cumene, which was proposed for the first time by Russian chemists.

Despite the quite a few methods available for the preparation of allocolchicinoids from natural colchicine, the potential introduction of this class of chemotherapeutic agents into clinical practice [49, 50] required the search for more economical methods and stimulated the development of approaches to the total synthesis of allocolchicine (**2**) and, first of all, NAC (**3**). The next Section is devoted to the principal strategies of forming the molecular skeleton of allocolchicinoids from commercially available chemicals.

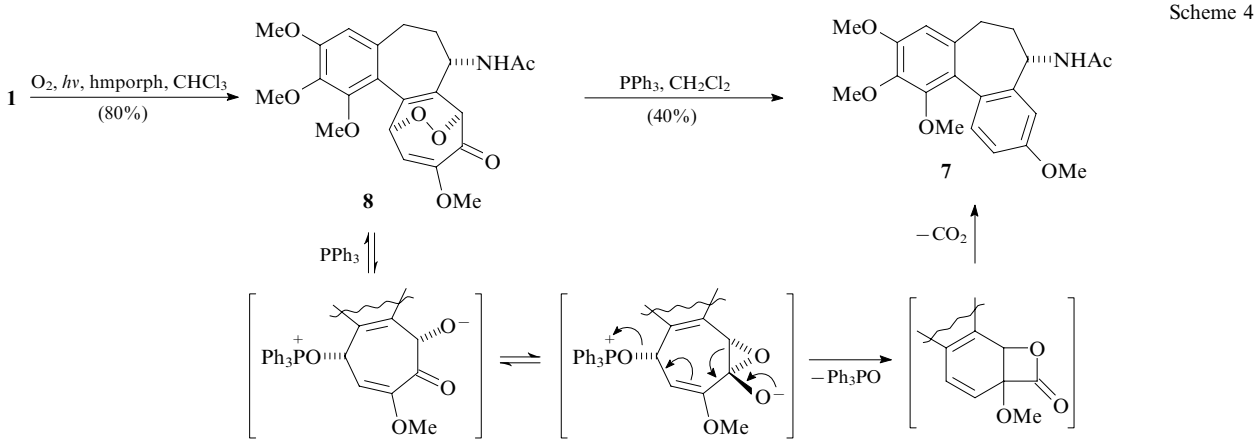
IV. Total syntheses of *N*-acetylcolchinol

1. Synthesis of *N*-acetylcolchinol using biaryl oxidative coupling

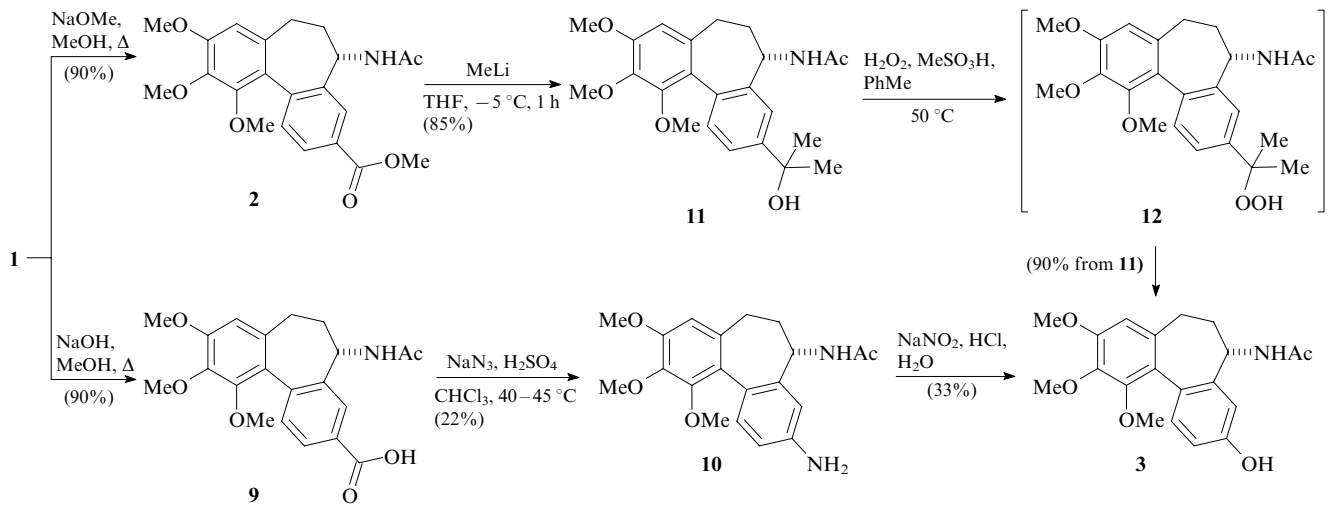
In 1988, Sawyer and Macdonald [51] performed the first total synthesis of racemic NAC (**3**) by using intramolecular nonphenolic oxidative coupling [52, 53] for the simultaneous formation of the aryl–aryl bond and seven-membered ring closure (Scheme 6).

3-(3,4,5-Trimethoxyphenyl)propionic acid (**13**) served as the initial substrate for the synthesis. The reduction of the carboxyl group to aldehyde group (compound **14**) and the subsequent addition of arylmagnesium bromide **15** resulted in racemic secondary alcohol **16**. The hydroxy group of **16** was converted to the *p*-toluenesulfonate group to be then replaced by an azide anion. Hydrogenation of azide **17** and acetylation of the resulting amine **18** produced substituted

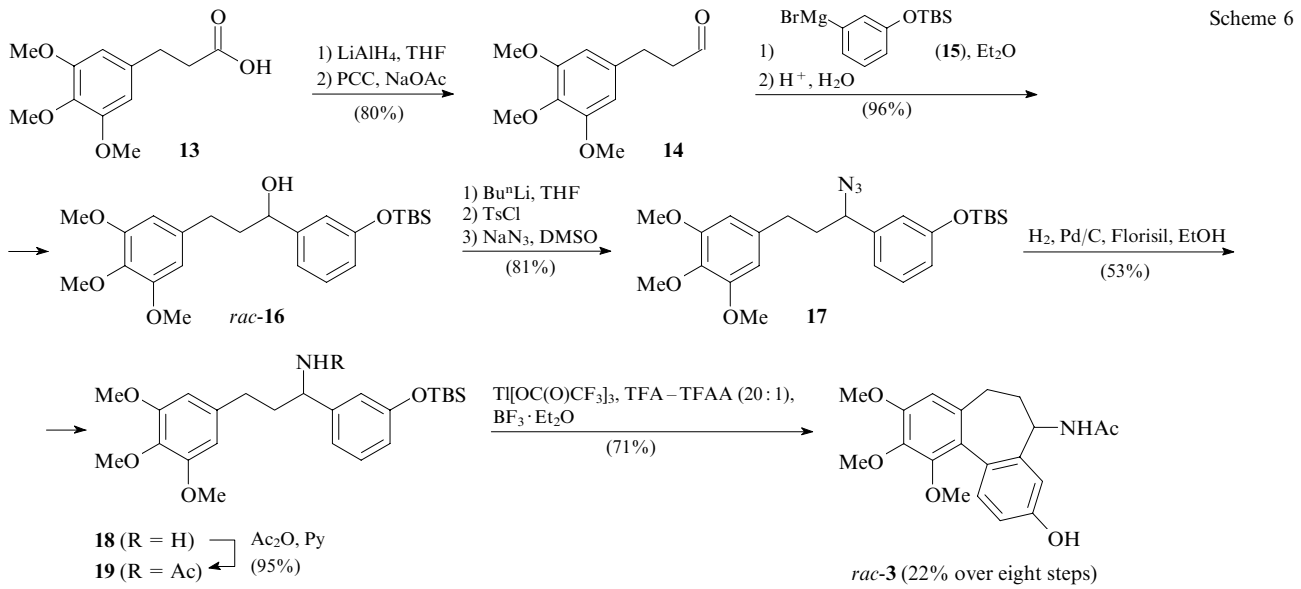
Scheme 4



Scheme 5

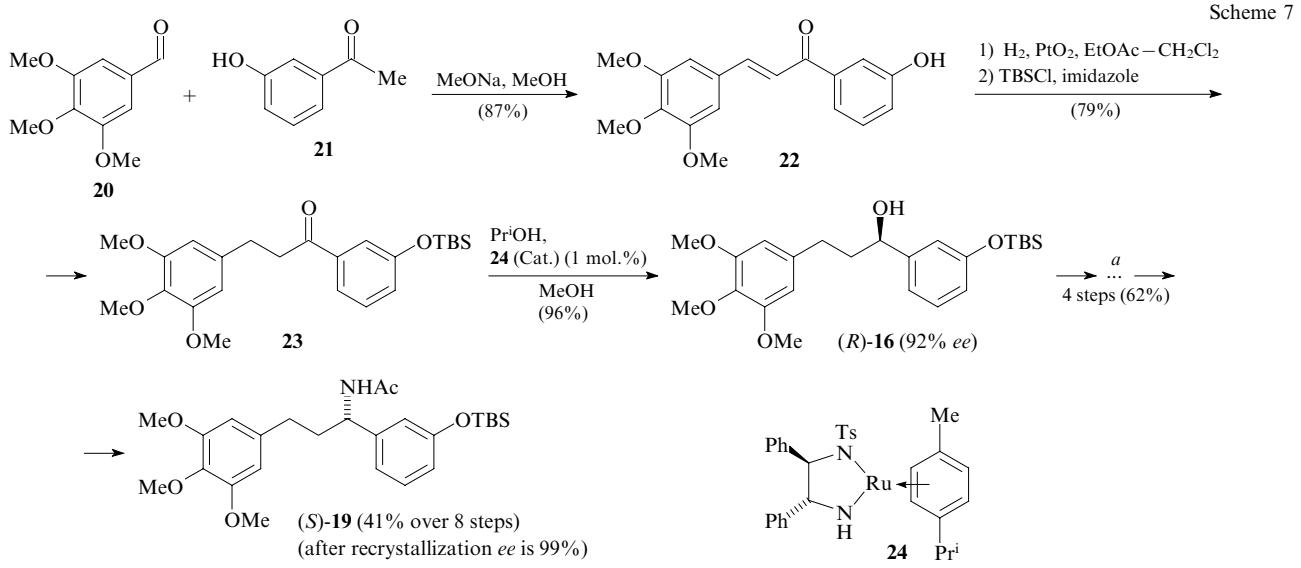


Scheme 6



PCC is pyridinium chlorochromate, TBS = Bu^tMe_2Si, Py is pyridine, TFA and TFAA are trifluoroacetic acid and trifluoroacetic anhydride, respectively

Scheme 7



(*a*) see Scheme 6: conditions for transformation of alcohol **16** to acetamide **19**

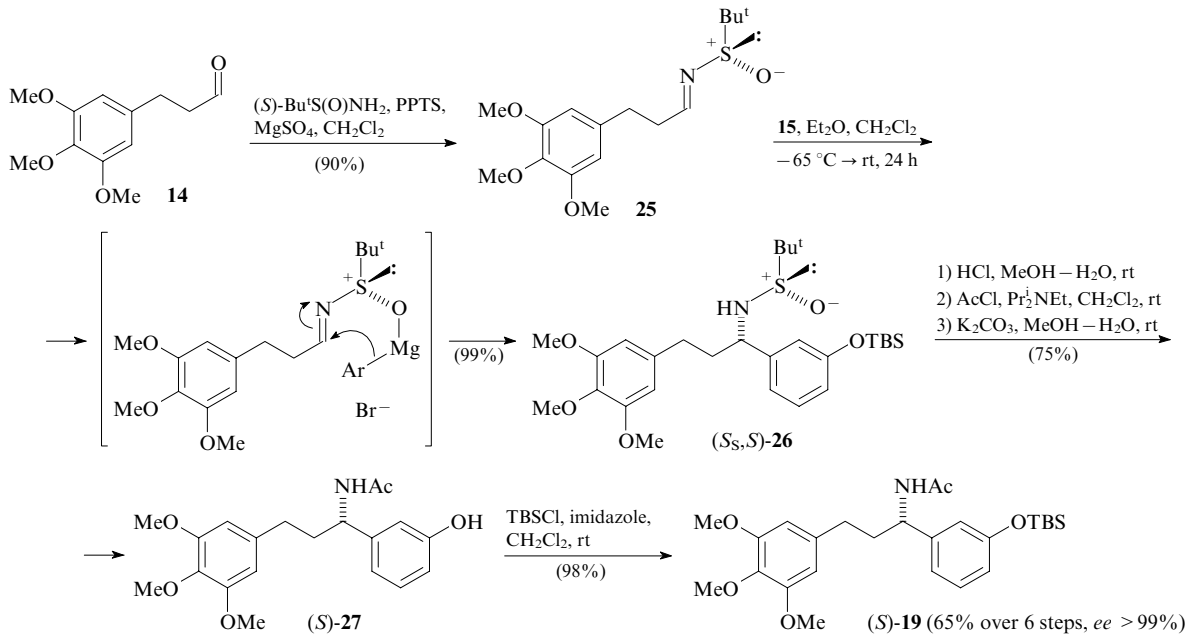
acetamide **19**. In the presence of a stoichiometric amount of thallium(III) trifluoroacetate,[52, 54] this product underwent intramolecular oxidative coupling giving rise to *rac*-NAC (*rac*-**3**). The authors demonstrated that no oxidative coupling takes place when the substrate is devoid of the *tert*-butyldimethylsilyl protecting group (TBS). The overall yield of the 8-step sequence was 22%.†

Taking the strategy proposed by Sawyer and Macdonald as a base, Kocienski and co-workers [56] developed an enantioselective version of the synthesis of (−)-NAC. In particular, they proposed two methods for the enantioselective preparation of the key intermediate **19** and modified the conditions of the oxidative coupling step.

According to the first method (Scheme 7),[56] the synthesis was started with crotonic condensation of 3,4,5-trimethoxybenzaldehyde (**20**) and *m*-hydroxyacetophenone (**21**), resulting in substituted chalcone **22**. Hydrogenation of the double bond of this compound in the presence of the Adams catalyst and TBS protection of the phenolic hydroxyl furnished ketone **23**, which is needed for the enantioselective introduction of the acetamide group. The asymmetric reduction of the carbonyl group of compound **23** was performed according to Noyori hydrogenation pattern.[57, 58] The use of the transfer hydrogenation conditions which were successfully applied by Schmalz's research group [12] in the course of colchicine **1** total synthesis, that is of isopropyl alcohol as a hydride donor and 1 mol.% of

† Subsequently several research groups reported that oxidative coupling according to Sawyer and Macdonald cannot be reproduced in a yield of more than ~30%.[30, 55]

Scheme 8



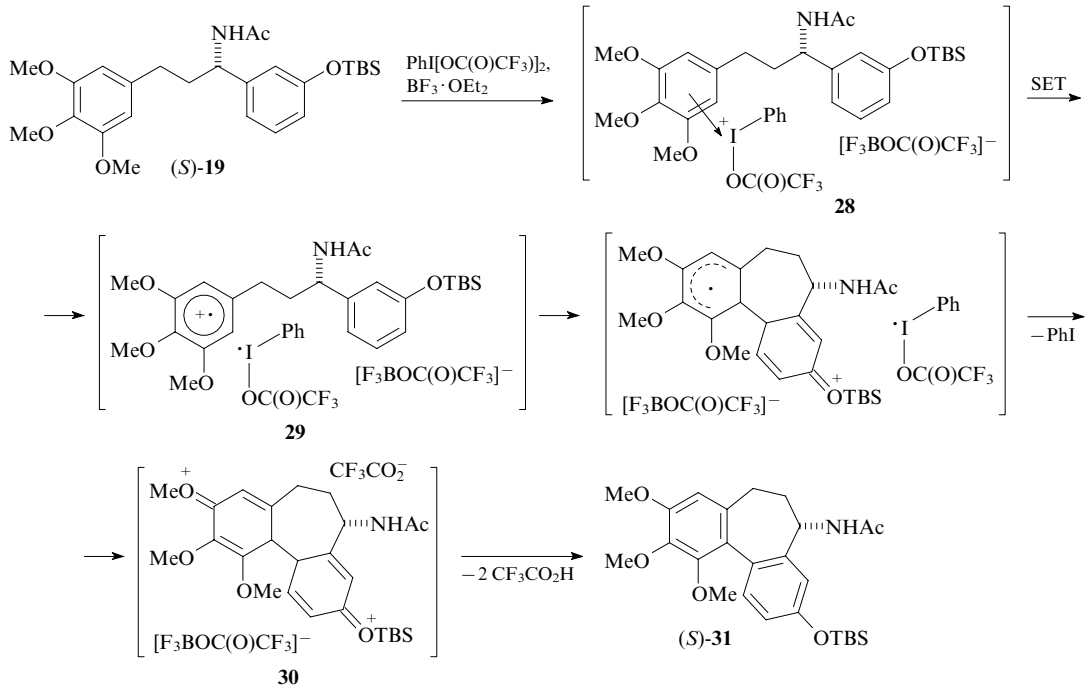
PPTS is pyridinium *p*-toluenesulfonate

[(1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethanediamino]-(η^6-*p*-cymene)ruthenium (**24**) as the catalyst,[59] afforded the reduction product (*R*)-**16** in 96% yield and 92% enantiometric excess. Alcohol (*R*)-**16** was then converted to 1,3-diarylpropylacetamide (*S*)-**19** by the Sawyer and Macdonald procedure (see Scheme 6).[51] After recrystallization, the enantiomeric purity of product **19** reached ~99%.

The second enantioselective synthesis of compound **19** proposed by the Kocienski's group[56] was based on the studies of nucleophilic addition to chiral sulfinylimines carried out by Ellman and co-workers.[60, 61] An advantage of this approach is the possibility of constructing the three-carbon chain between the aryl moieties and enantioselective introduction of the second amino group into compound **19** in one step (Scheme 8).

According to the proposed method, sulfinylimine **25** obtained by condensation of aldehyde **14** and (*S*)-*tert*-butylsulfinylamide[62] was used in the nucleophilic addition of arylmagnesium bromide **15** to give a chromatographically separable mixture of diastereomeric adducts **26**. The diastereomer ratio in the mixture was 94 : 6, the target (S_S,*S*)-diastereomer being the major component; the stereochemistry of the reaction products was consistent with the theoretical model of chelation control of the reaction proposed by Ellman.[61] This was followed by acid hydrolysis of the *tert*-butylsulfinyl moiety accompanied by side depro-

Scheme 9



tection of the phenolic hydroxyl. N-,O-Acylation of the resulting aminophenol with acetyl chloride in the presence of di(isopropyl)ethylamine followed by selective *O*-deacetylation on treatment with a potassium carbonate solution in aqueous ethanol produced *N*-acetylated derivative **27**. The repeated *tert*-butyldimethylsilyl protection of the phenolic hydroxyl in **27** yielded intermediate **19**.

1,3-Diarylpropylacetamide **19** was then introduced into the oxidative coupling reaction. It is known from a publication of Tohma and Kita [63] that the oxidative coupling of phenols and alkyl ethers of phenols efficiently proceeds in the presence of hypervalent iodine compounds activated by Lewis acids. Therefore, phenyliodonium bis(trifluoroacetate)–boron trifluoride etherate system was used to carry out cyclization (Scheme 9).

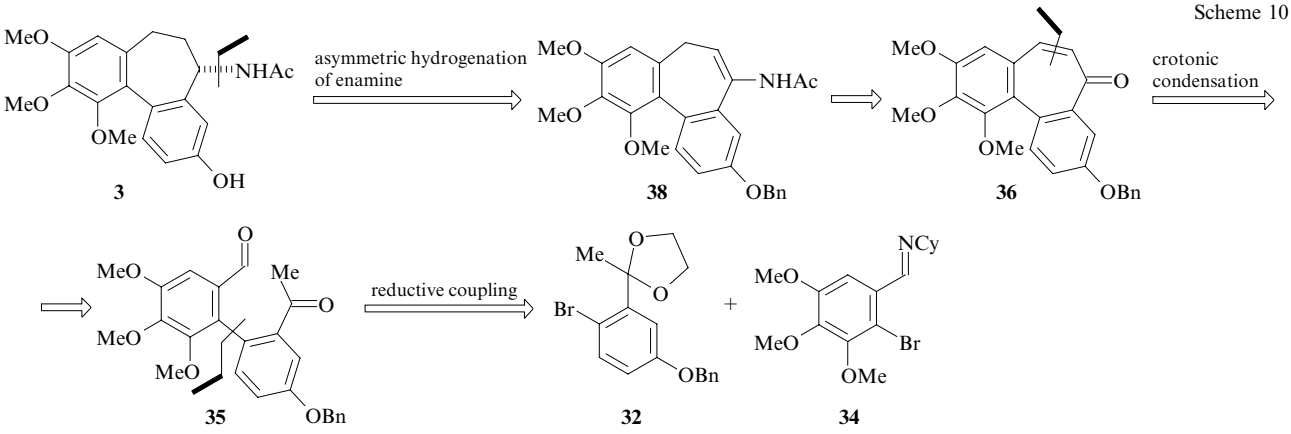
Presumably,[56] the reaction follows a radical ion mechanism. The formation of π-complex **28** of the trimethoxy-substituted aryl group with the iodonium cation and subsequent single electron transfer (SET) yield radical cation **29**. This intermediate is then cyclized and oxidized to dication **30**, which is being doubly deprotonated to give the target coupling product **31**. This reaction mechanism is supported by EPR studies carried out by Kita *et al.*[64]

2. Synthesis of *N*-acetylcolchinol using biaryl reductive coupling

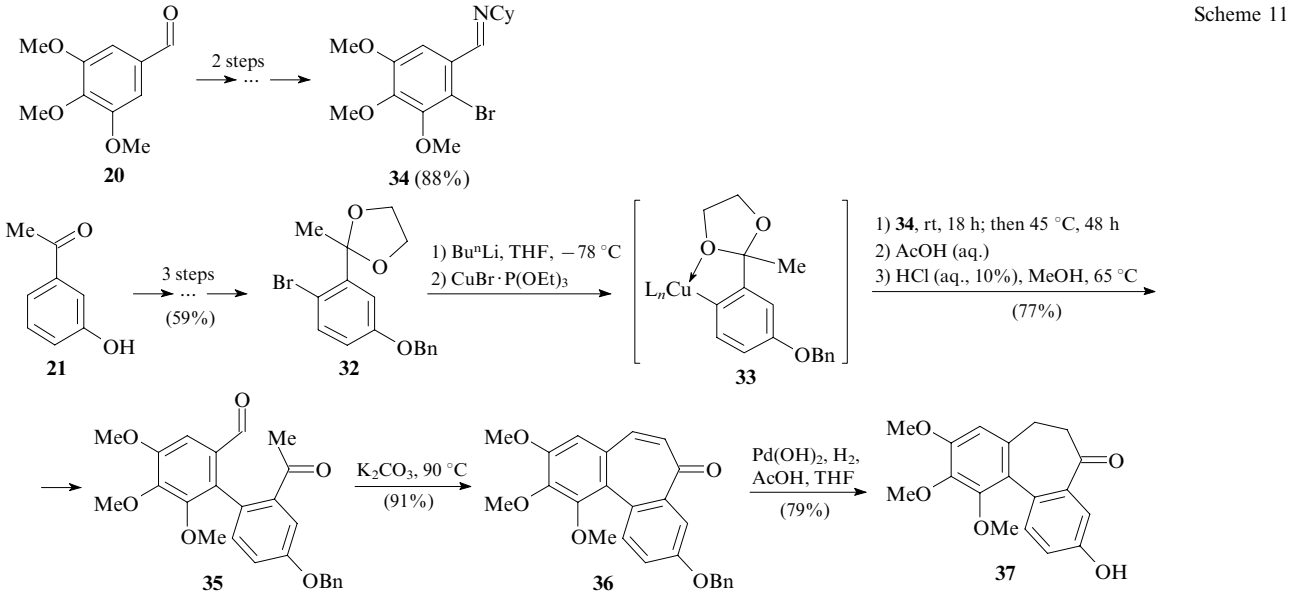
In 2007, a group of researchers from the research department of the AstraZeneca company engaged in the preclinical trials of the ZD6126 (**4**) prodrug of (−)-*N*-acetylcolchinol reported an alternative synthetic approach to (−)-NAC (**3**).[55] The authors applied a modified Ullmann reaction [65–68] to form the aryl–aryl bond, crotonic condensation to close the seven-membered ring, and ruthenium-catalyzed asymmetric hydrogenation of enamine [69] to introduce the C(7) stereocentre (Scheme 10 shows the retrosynthetic analysis). The Ullmann reaction was chosen for the formation of the biaryl moiety of (−)-NAC (**3**) relying on the publication by Ziegler *et al.*,[68] who proposed conditions for the reductive cross-coupling of aryl halides with coordinating substituents (acetal and thioacetal groups) in the *ortho*-position to the halogen.

The synthesis was started from the transformation of aryl bromide **32** to monocuprate **33** by halogen–lithium exchange and transmetallation reactions (Scheme 11).[70] Compound **33** was utilized *in situ* in the reductive coupling with *N*-cyclohexylimine **34**, and after that, acid hydrolysis of the imine and acetal groups was performed. The base-

Scheme 10

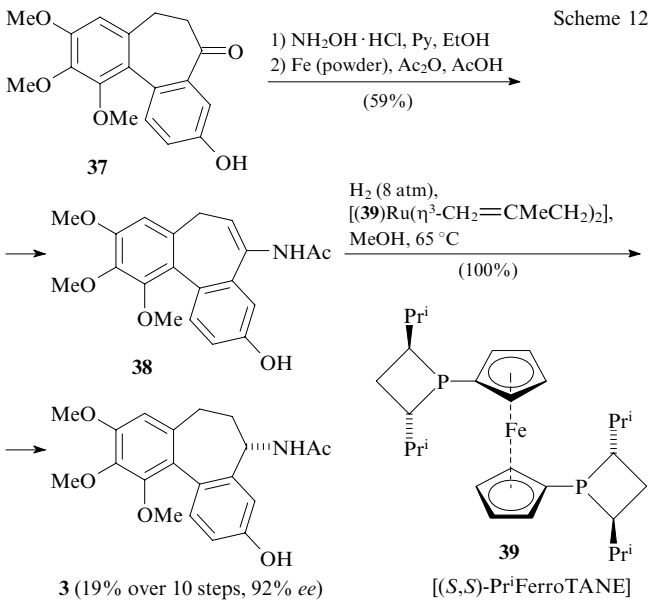


Scheme 11



Cy is cyclohexyl

Scheme 12



catalyzed intramolecular crotonic condensation of the biaryl **35** thus formed afforded enone **36**, which had the desired tricyclic structure. The catalytic hydrogenation of the double bond of compound **36** was accompanied by removal of the benzyl protection of the phenolic hydroxyl, giving rise to ketone **37**.

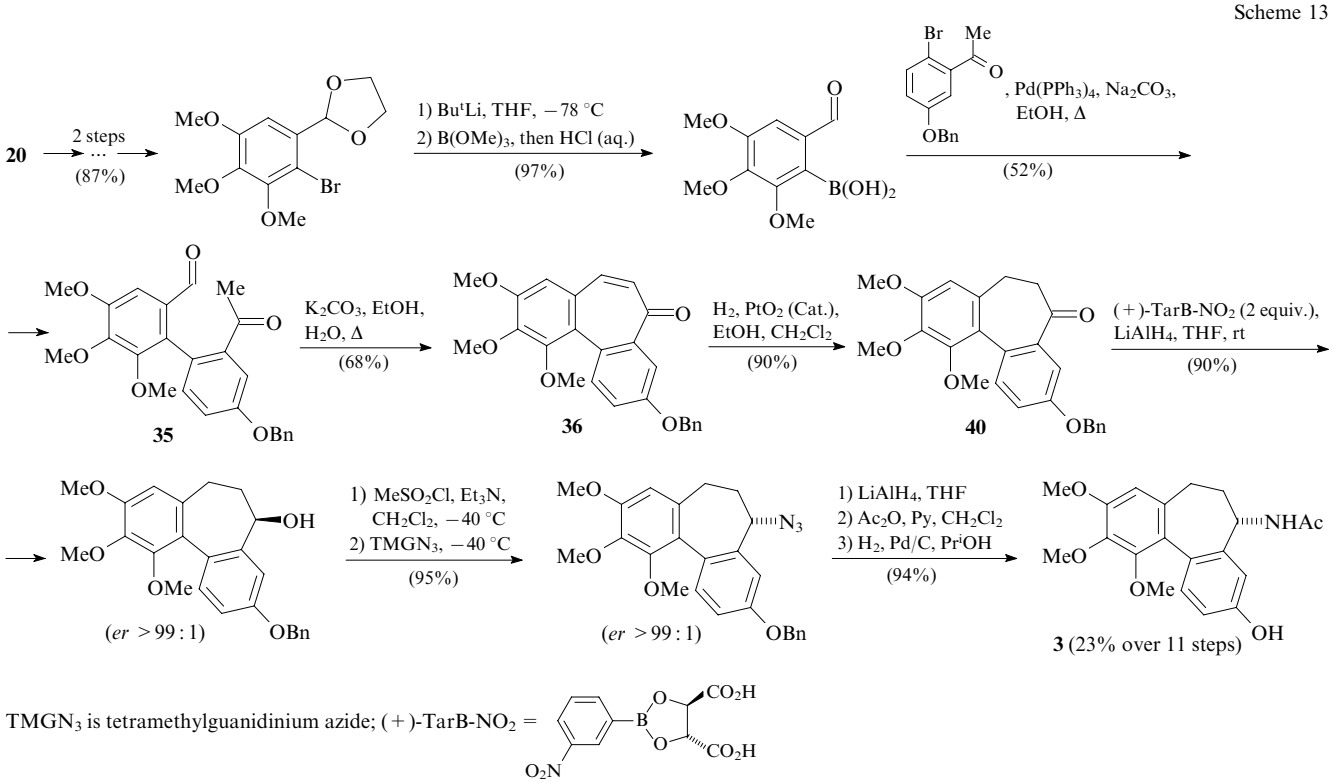
This was followed by the enantioselective introduction of the acetamide group at C(7). For this purpose, ketone **37** was converted to enamide **38** by condensation with hydroxylamine and reduction – acylation by the iron(0) – acetic acid – acetic anhydride system (Scheme 12).[71] Product **38** was used in the catalytic asymmetric hydrogenation. Since there are only a few reported cases of enantioselective reduction of seven-membered endocyclic enamides,[72, 73] the authors screened the catalytic activity of 42 ruthenium, iridium and rhodium complexes.[69] They found that the complex [(**39**)Ru(η^3-CH_2=$CMeCH_2$)$_2$] taken as the catalyst in 1 : (500 – 1000) ratio to the substrate provides the target (−)-NAC (**3**) in a quantitative yield and *ee* 92% (see Scheme 12). Thus, the overall yield of the 10-step sequence starting from the commercially available *m*-hydroxyacetophenone (**21**) was 19%.

A year later, Kocienski's group[30] reported their third asymmetric synthesis of (−)-NAC (**3**) (Scheme 13), which followed the same strategy and started from the same reactants as the method developed by the AstraZeneca team (see Schemes 11, 12) but differed by the implementation.

Distinctive features of this synthesis include the use of the Suzuki – Miyaura cross-coupling[65, 74] for the construction of the biaryl moiety of compound **35**,‡ selective catalytic hydrogenation of the double bond of enone **36** with retention of the benzyl protection of the phenolic hydroxyl and application of the chiral Lewis acid (+)-TarB-NO_2 based on L-tartaric acid for asymmetric reduction of the carbonyl group of ketone **40**.[26, 78] This reaction sequence furnished (−)-NAC (**3**) in 11 steps in 23% yield and enantiomeric excess of > 99%.

‡ Other examples of the use of Suzuki cross-coupling in the synthesis of colchicine and allocolchicine analogues that have not been included in this review can be found in Refs 75 – 77.

Scheme 13

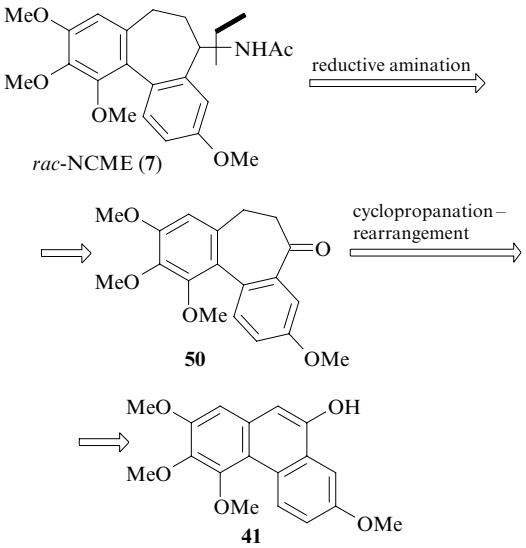


$TMGN_3$ is tetramethylguanidinium azide; (+)-TarB-NO_2 =

3. Synthesis of *N*-acetylcolchinol *O*-methyl ether using cyclopropanation–ring expansion reaction of substituted phenanthrol

In 2006, DeShong's group [28] from the University of Maryland reported the synthesis of racemic NCME (**7**) based on a conceptually novel approach to the preparation of allocolchicines. The authors used ring expansion reaction of substituted phenanthrol **41** as the key step for the construction of NCME carbocyclic skeleton (Scheme 14 shows the retrosynthetic analysis).

Scheme 14



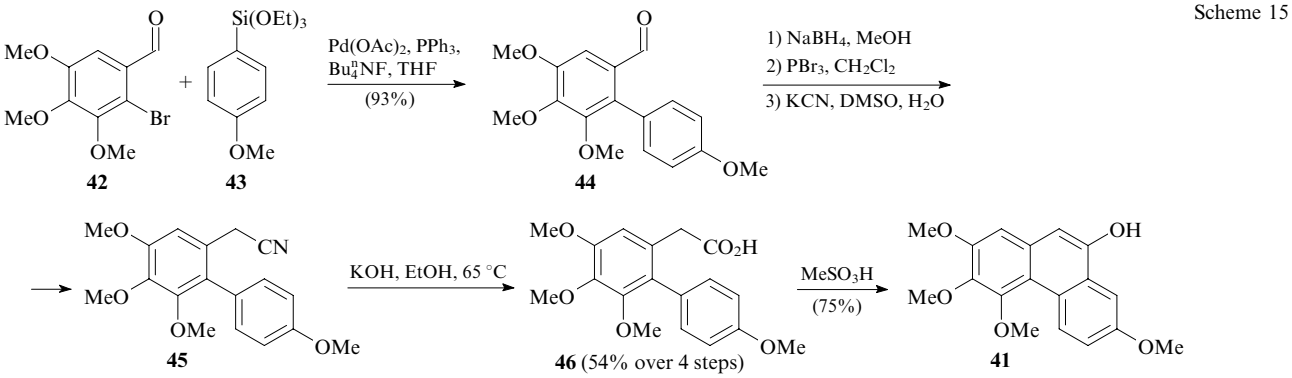
Compound **41** was prepared from 2-bromo-3,4,5-trimethoxybenzaldehyde (**42**) in 6 steps (Scheme 15). The palladium-catalyzed cross-coupling of aryl bromide **42** and arylsiloxane **43** [79] produced biaryl **44**. For introducing the lacking carbon atom, the aldehyde group in compound **44** was reduced by sodium borohydride, and then the hydroxy group was replaced by the nitrile group in two steps. Base hydrolysis of the resulting nitrile **45** afforded carboxylic acid **46**, which underwent intramolecular Friedel–Crafts cyclization induced by methanesulfonic acid to give phenanthrol **41**.

The hydroxy group of phenanthrol **41** was protected by the methoxymethyl group (Scheme 16), and then product **47** was cyclopropanated with dichlorocarbene formed *in situ*. The resulting norcaradiene **48** rearranged with cyclopropane ring opening in an acidic medium to give chloro enone **49** containing the target 6,7,6-tricyclic system. The catalytic hydrogenation of the vinyl chloride group under conditions reported by Coburn and Jones [80] ended in the formation of ketone **50**, which was converted to the target *rac*-NCME (**7**) by reductive amination [81] and acylation with acetic anhydride. The overall yield of the 12-step sequence was 8%.

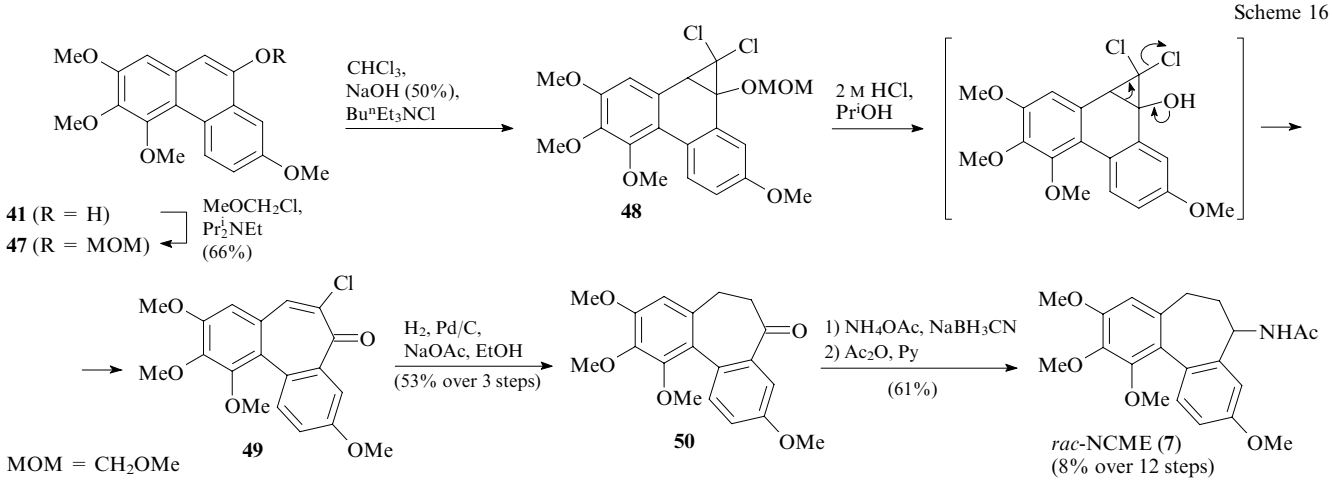
4. Synthesis of *N*-acetylcolchinol *O*-methyl ether using the Nicholas reaction

Green's group [29, 82, 83] proposed a strategy for the synthesis of NCME (**7**) using intramolecular Nicholas reaction for the construction of the seven-membered ring. As the starting reactants, the authors used commercially available 2-bromo-5-methoxybenzaldehyde (**51**) and 2,3,4-trimethoxyphenylboronic acid (**52**) (Scheme 17). The Suzuki–

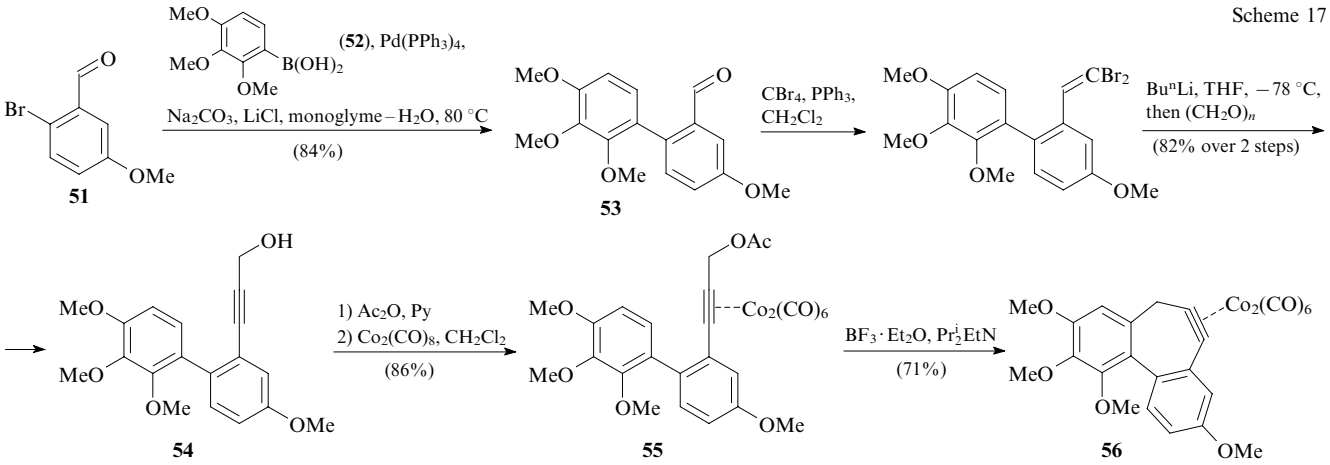
Scheme 15



Scheme 16



Scheme 17

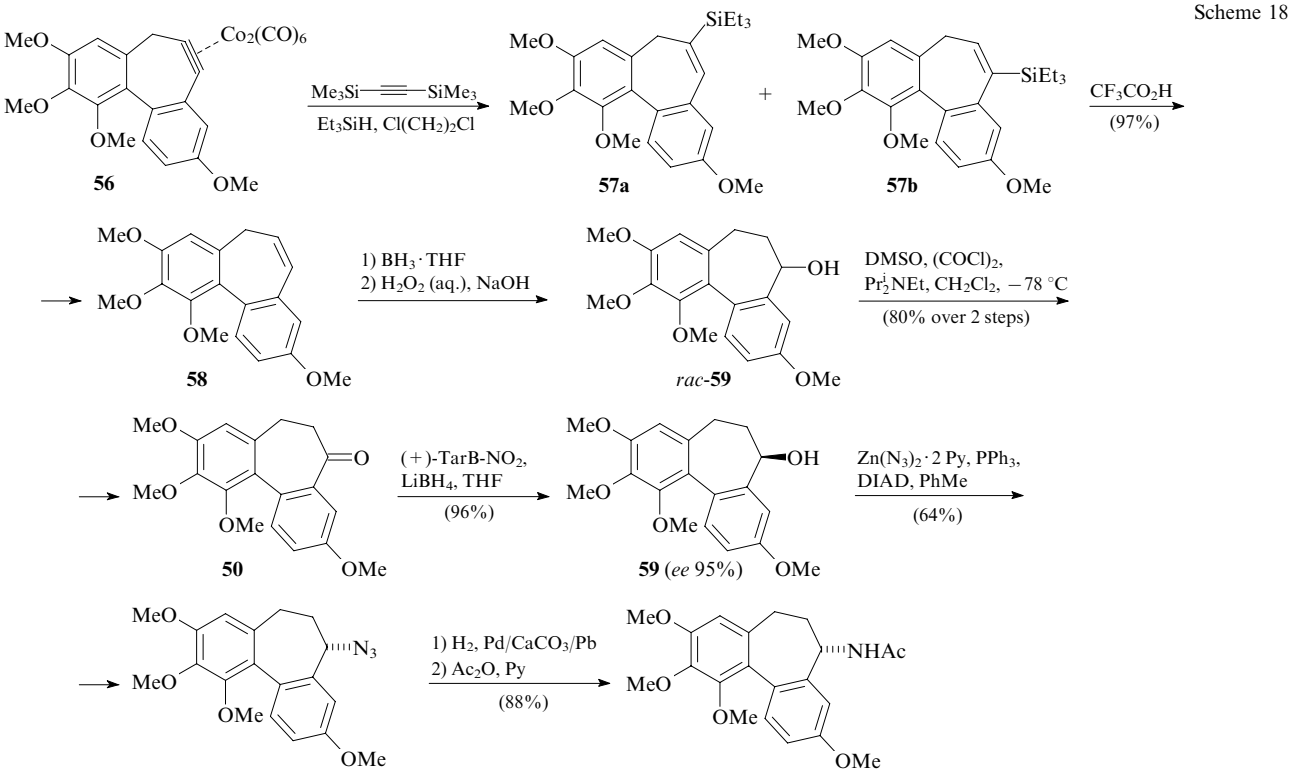


Miyaura cross-coupling [65, 75] of compounds **51** and **52** under the conditions reported by Fürstner and co-workers [84] afforded substituted benzaldehyde **53**. This compound was converted to substituted propargyl alcohol **54** by the Corey – Fuchs reaction [47, 85] with subsequent trapping of the formed lithium acetylenide by paraformaldehyde. Acetylation of alcohol **54** and complexation with octacarbonyldicobalt(II) produced substrate **55** required for the Nicholas cyclization. The cyclization of complex **55** was induced by boron trifluoride etherate in the presence of diisopropylethylamine (to bind acetic acid formed in the reaction).

After cyclization, the hexacarbonyldicobalt moiety was split off according to the procedure developed by Isobe and co-workers [86] (Scheme 18). Hydrosilylation of compound **56** with triethylsilane in dichloroethane produced a mixture of vinylsilane isomers **57a**,**b** and hexacarbonyldicobalt(II), which was trapped by adding bis(trimethylsilyl)acetylene. Desilylation of derivatives **57a**,**b** *in situ* on treatment with trifluoroacetic acid ended in the formation of dibenzocycloheptene **58**, which was subjected to hydroboration – oxidation to be converted to racemic alcohol **59**. The Swern oxidation of this product afforded ketone **50**.[47] The subsequent transformations of the functional group at C(7),§ including enantioselective reduction of the carbonyl group of ketone **50** using the Lewis acid (+)-TarB-NO_2,[78] the Mitsunobu S_N2 substitution of an azide group for the hydroxyl,[47] hydrogenation of the azide group in the presence of the Lindlar catalyst and acyalation of the amine thus formed with acetic anhydride yielded the target

§ This synthetic sequence for enantioselective transformation of the carbonyl group into acetamide group was first used by Wulff and co-workers [36] in 2003 in the synthesis of (−)-allocolchicine (**2**).

Scheme 18



DIAD is diisopropyl azodicarboxylate

(−)-(*S*)-NCME (**7**). The overall yield of the sequence comprising 13 steps was 18%, and the enantiomeric excess of the product was 93%.

Later, these authors demonstrated the applicability of this synthetic approach to the preparation of (−)-allocolchicine (**2**) and some of its structural analogues.[87]

V. Methods for the synthesis of allocolchicine

1. Synthesis of allocolchicine from 7,8,9-trimethoxybenzosuberone using the Diels – Alder cycloaddition

The first total synthesis of allocolchicine (**2**) was performed in 2003 at the University of Michigan by the research group headed by Wulff.[26] As the starting reactant, the authors used the benzosuberone **60**, which already contained the bicyclic **AB** system of allocolchicine (**2**) (Scheme 19). For constructing the lacking ring **C**, the Diels – Alder reaction followed by aromatization of the resulting adduct was used. More recently, the same strategy was utilized to prepare the structural analogues of allocolchicine with different sets of substituents in ring **C**.[26]

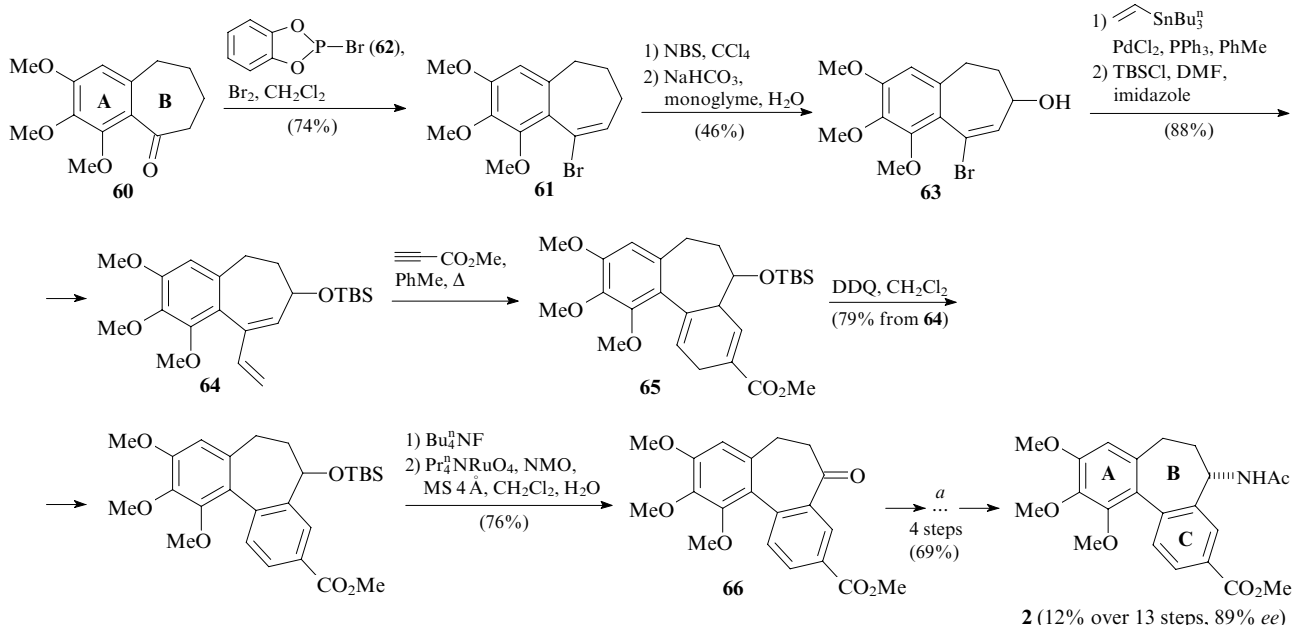
The first stage was transformation of benzosuberone **60** into vinyl bromide **61** by the reaction with bromine in the presence of a stoichiometric amount of 2-bromobenzo-1,2,3-dioxaphosphole (**62**) (see Scheme 19).[88] For introduction of the allocolchicine functional group at the C(7) atom, radical allylic bromination of derivative **61** with *N*-bromosuccinimide (NBS) was carried out, and after that, the resulting allyl bromide was hydrolyzed to allyl alcohol **63**. The Stille cross-coupling[65, 89] of this alcohol with tributylvinylstannane completed the construction of the diene system. After cross-coupling, the allylic hydroxy group was protected by the bulky *tert*-butyldimethylsilyl group to control the regioselectivity of the key Diels – Alder reaction. The cycloaddition of diene **64** and methyl propynoate occurred in boiling toluene and gave tricyclic adduct **65**, which was aromatized under the action of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Ref. 90, p. 215). The removal of the TBS protection on treatment with tetrabutyl ammonium fluoride followed by oxidation of the hydroxy group with *N*-methylmorpholine oxide (NMO) in the presence of a catalytic amount of ruthenium(VII) (Ley reaction)[47, 91] resulted in ketone **66**, which was converted to (−)-allocolchicine (**2**) similarly to conversion of ketone **50** to acetamide **7** (see Scheme 18). The overall yield of this sequence of 13 reactions was 12%, the enantiomeric excess of the product was 89% (99% *ee* after recrystallization).

It is known that (7*S*)-allocolchicinoids [(−)-allocolchicine (**2**), (−)-NAC (**3**), (−)-NCME (**7**)] are effective antitumour agents.[2, 23, 24, 42] Studies by NMR spectroscopy indicate that allocolchicinoids **2**, **3** and **7** exist in solution as equilibrium mixtures of (a*R*,7*S*) and (a*S*,7*S*) diastereomers (see Section II). However, it has not been elucidated as yet what is the axial chirality of the biologically active isomer able to bind to tubulin.

In order to obtain analogues of allocolchicine (**2**) having a fixed axial configuration, Wulff and co-workers modified the synthetic route described above (see Scheme 19). Based on their considerable research experience in the field of Fischer carbene chemistry,[92 – 94] they utilized the Dötz benzannulation[47, 95] to construct the polysubstituted ring **C** of allocolchicinoids.[34, 36]

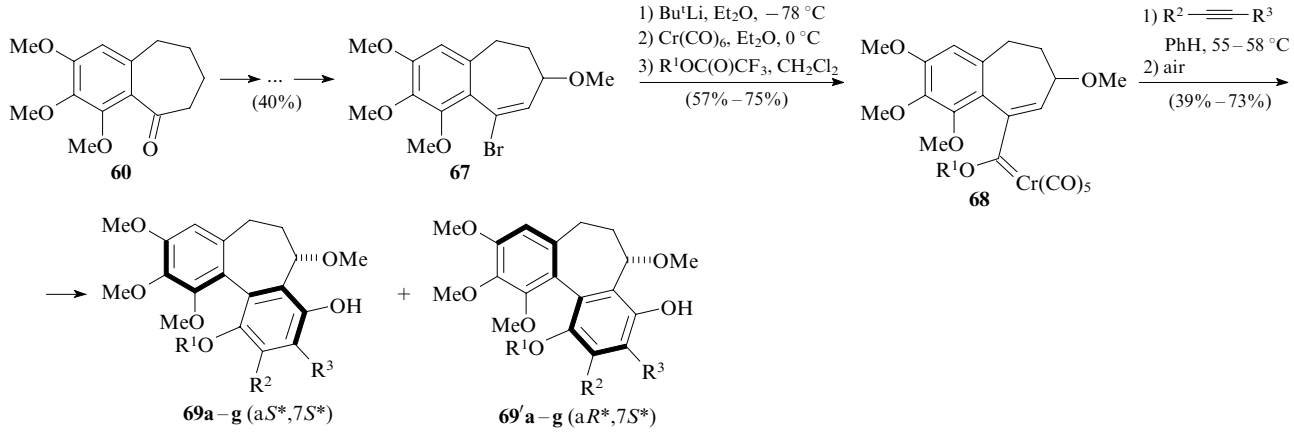
The synthesis of allocolchicine analogues using Dötz benzannulation was started with the transformation of benzosuberone **60** into vinyl bromide **67** (Scheme 20) by a strategy similar to that used to convert **60** to vinyl bromide **63** (see Scheme 19).[34] A number of carbene complexes **68** were prepared from compound **67** by the standard Fischer method.[95] The Dötz benzannulation of chromium complexes **68** with substituted alkynes followed by oxidative demetallation with air oxygen yielded a mixture of diastereomeric products **69** and **69′** with high diastereoselectivity towards (a*S**,7*S**)-diastereomer **69** (see Scheme 20). The configuration of the major diastereomer was established by X-ray diffraction analysis. The authors proposed a model that accounts for the appearance of asymmetric induction in the reaction (effect of the configuration of the

Scheme 19



(*a*) see Scheme 18: conditions for the transformation of ketone **50** to acetamide **7**; MS are molecular sieves

Scheme 20



Compounds **69**, **69′**	R^1	R^2	R^3	Overall yield (%)	*dr* (**69** : **69′**)
a	Me	H	Pr^n	40	only **69**
b	Et	H	Pr^n	73	13 : 1
c	Pr^i	H	Pr^n	72	12 : 1
d	Et	H	Me_3Si	45	only **69**
e	Et	H	Ph	39	only **69**
f	Et	H	Bu^t	43	only **69**
g	Et	Et	Et	58	only **69**

asymmetric carbon atom on the axial configuration of the biaryl moiety).[36]

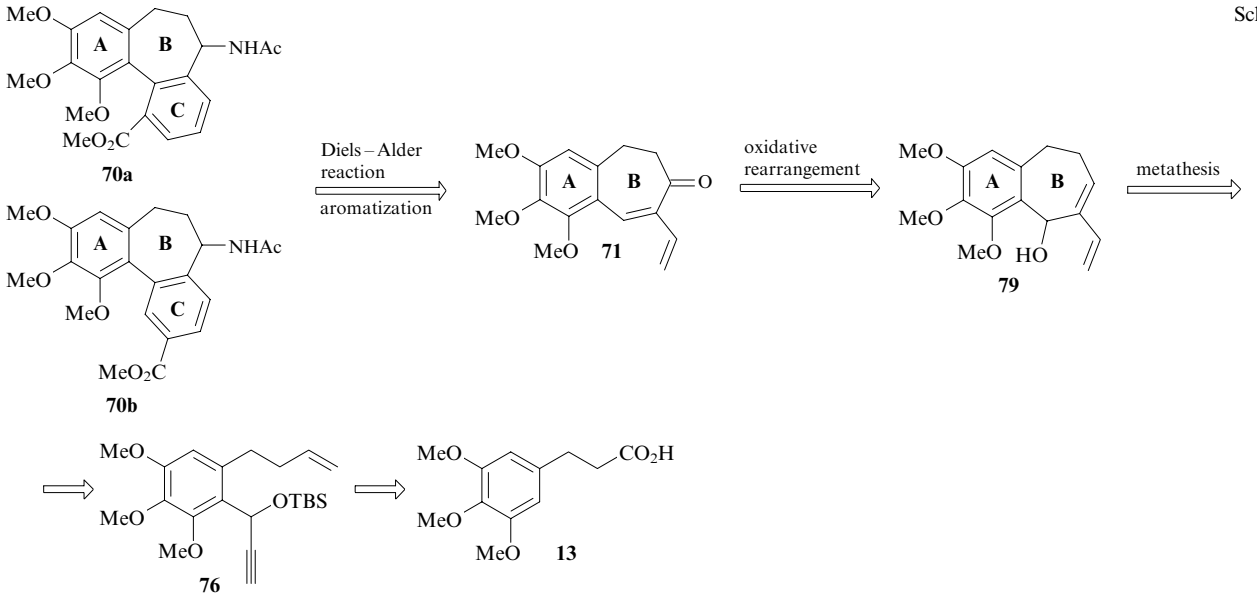
Data on the biological activity of the structural analogues of allocolchicine **69** and **69′** have not been reported to date.

2. Synthesis of allocolchicinoids using the metathesis and Diels – Alder reactions

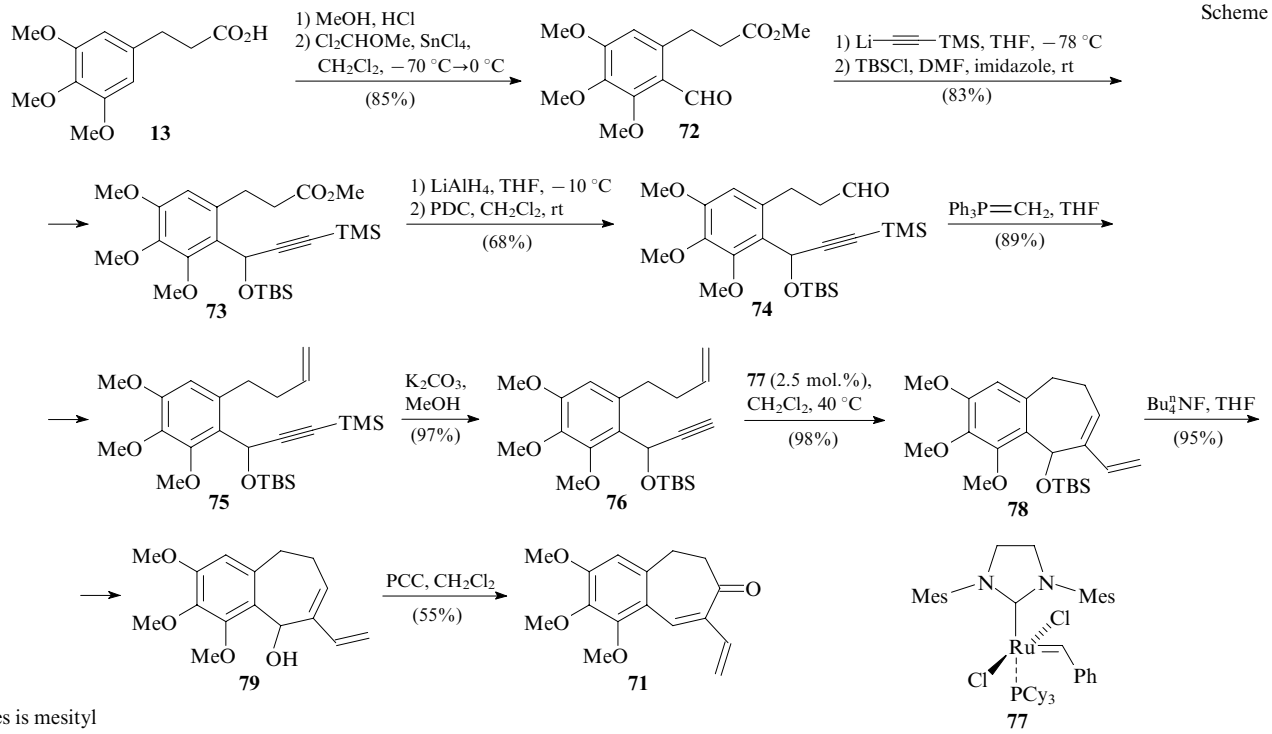
The studies of Wulff and co-workers on the application of the Diels – Alder reaction in the synthesis of allocolchicines were further developed by French scientists Boyer and Hanna.[31] While following Wulff's strategy for the construction of the ABC-tricyclic system according to the **AB** → **ABC** pattern, Boyer and Hanna used the [4 + 2]-cycloaddition to obtain structural analogues of allocolchicine **70a**,**b** with an altered position of the ester group in ring **C** (the retrosynthetic analysis is presented in Scheme 21). A distinctive feature of the synthesis is the use of ring closure metathesis[96,97] and the Dauben oxidative rearrangement of allyl alcohols[98,99] to construct the key intermediate **71** (see Scheme 21).

Commercially available 2-(3,4,5-trimethoxyphenyl)propionic acid (**13**), which was used previously in the synthesis of colchicinoids, served as the starting substrate (see Scheme 6). First, compound **13** was converted to aldehyde **72** *via* esterification and formylation of dichloromethyl methyl ether (Scheme 22).[100] Then product **72** was alkynylated with lithium trimethylsilylacetylenide, and the

Scheme 21



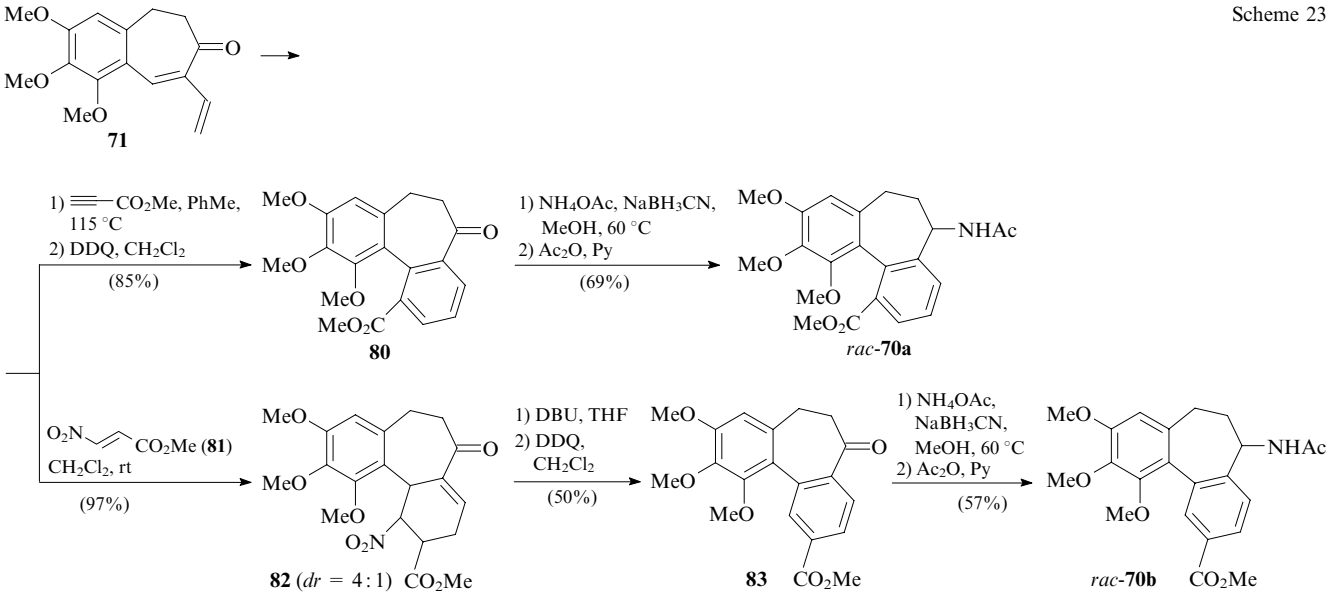
Scheme 22



hydroxy group of the alcohol thus formed was protected with the *tert*-butyldimethylsilyl moiety. For introducing the alkenyl chain, ester **73** was converted to the corresponding aldehyde **74** by successive reduction with lithium aluminium hydride and oxidation with pyridinium dichromate (Cornforth reagent, PDC);[47] then aldehyde **74** was introduced into the Wittig reaction with methylidenetriphenylphosphorane to give alkene **75**. The removal of the trimethylsilyl protection from the triple bond of enyne **75** by treatment with potassium carbonate in methanol completed the synthesis of substrate **76** necessary for the formation of a seven-membered ring according to the metathesis reaction.

The intramolecular metathesis of enyne **76** (see Scheme 22) proceeded in the presence of 2.5 mol.% of the second-generation Grubbs catalyst **77** (Ref. 101) and afforded product **78** incorporating the **AB** moiety of the tricyclic system that is present in the target allocolchicinoid molecules. The lacking ring **C** was constructed by the Diels – Alder reaction; for this purpose **78** was converted to diene **71**. First, the silyl protecting group present in derivative **78** was removed by treatment with tetrabutylammonium fluoride to yield allyl alcohol **79**. Oxidation of **79** with pyridinium chlorochromate [102] further induced Dauben oxidative sigmatropic rearrangement, resulting in the formation of the desired diene **71**.

Scheme 23



DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

Allocolchicinoid **70a** was prepared from diene **71** in 4 steps (Scheme 23). The first step was the Diels – Alder reaction of derivative **71** with methyl propiolate in boiling toluene. The cycloaddition product was treated with 2,3-dichloro-5,6-dicyanobenzoquinone, which induced aromatization [90] yielding tricyclic derivative **80**. The reductive amination of the latter by the ammonium acetate – sodium cyanoborohydride system [81] and acylation of the amine thus formed with acetic anhydride completed the synthesis of the target *rac*-**70a**. The authors noted that this compound formed as a mixture of two atropoisomers (in 2 : 1 ratio), which can be separated by chromatography on silica gel. This fact attests to a high energy barrier for atropoisomerization.

In turn, allocolchicinoid **70b** was prepared from diene **71** in five steps (see Scheme 23). As the dienophile, the authors used methyl 3-nitroacrylate (**81**) in order to invert the regioselectivity of the Diels – Alder reaction.[103] The cycloaddition of compounds **71** and **81** smoothly proceeded in dichloromethane at room temperature to give only one regioisomer **82**, which formed as a mixture of diastereomers in 4 : 1 ratio. Elimination of the nitro group of derivative **82** induced by an amidine base and oxidation of the elimination product with 2,3-dichloro-5,6-dicyanobenzoquinone led to aromatic ketone **83**, which was converted to target allocolchicinoid *rac*-**70b** by reductive amination and *N*-acetylation. According to NMR spectroscopic data, *rac*-**70b** was obtained as a mixture of two rotamers, which exist in dynamic equilibrium in solution at room temperature.

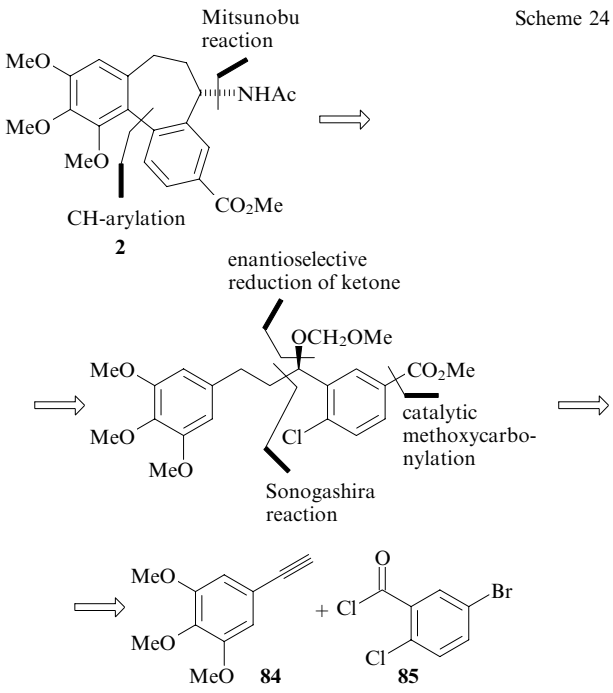
The authors studied the antitubulin activities of the prepared allocolchicinoids. Whereas derivative *rac*-**70a** proved to be inactive, allocolchicinoid *rac*-**70b** inhibited tubulin polymerization when present in the same concentration as the natural colchicine (**1**).

The synthetic strategy described above was adjusted to prepare allocolchicine analogues with eight-membered ring **B**.[31]

3. Synthesis of allocolchicine using direct catalytic CH-arylation

One of the few examples of the use of direct catalytic CH-arylation [104 – 108] in the synthesis of natural compounds [27, 109 – 113] is the preparation of allocolchicine (**2**) reported by Leblanc and Fagnou [27] in 2005.

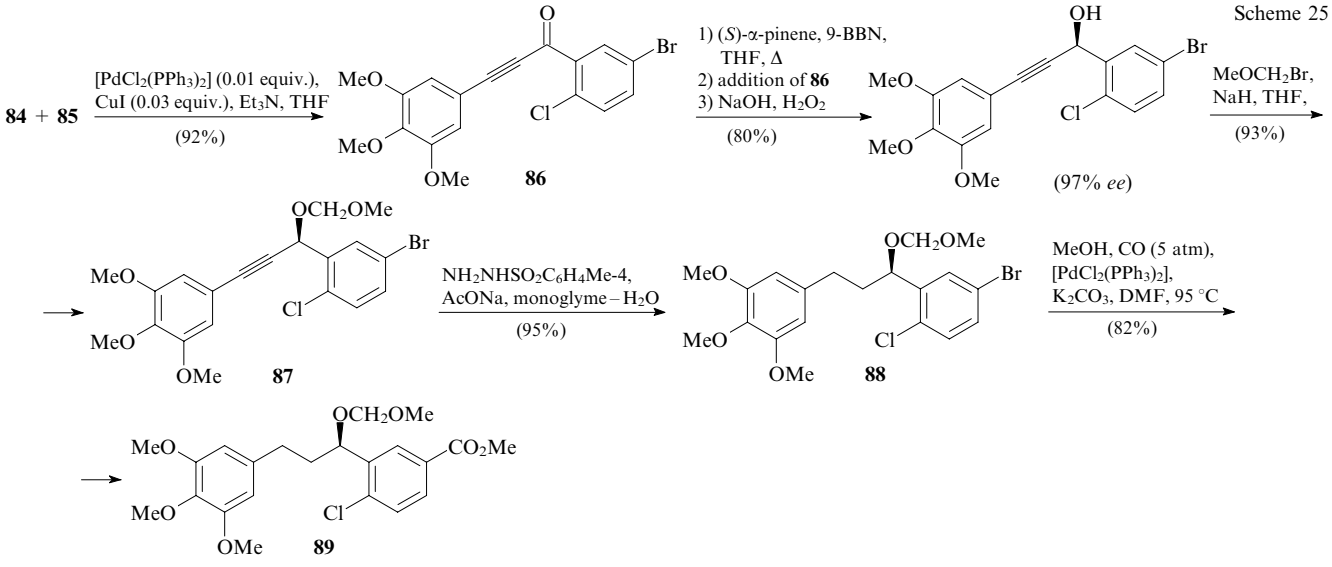
Scheme 24



The retrosynthetic analysis (Scheme 24) proposed by the authors is based on the assumption that the carbocyclic skeleton of alkaloid **2** can be constructed starting from alkyne **84** and acyl chloride **85** by halogen-selective cross-coupling, methoxycarbonylation, and direct intramolecular CH-arylation of the electron-excessive 3,4,5-trimethoxyphenyl moiety.

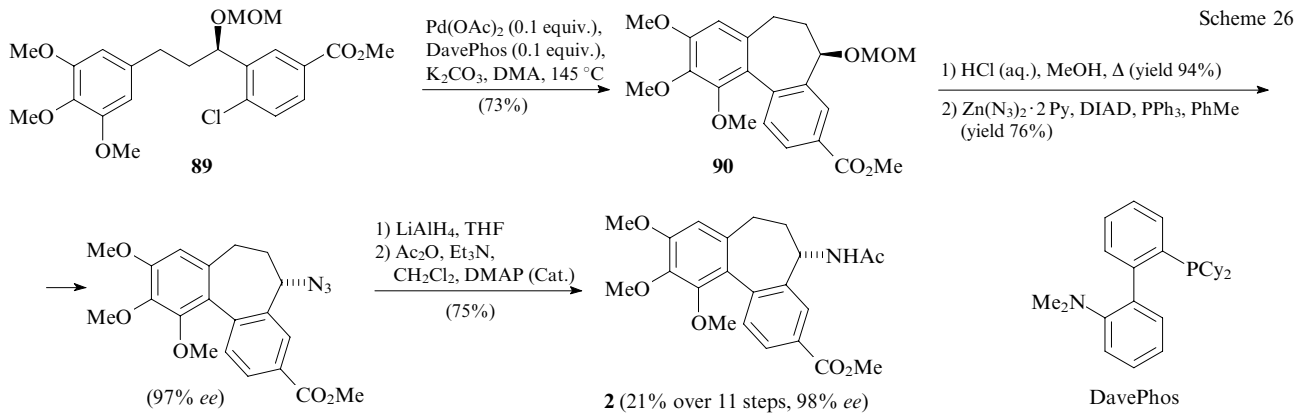
The synthesis was started with the Sonogashira cross-coupling of alkyne **84** and acyl chloride **85** (Scheme 25).[65, 114] The carbonyl group of the coupling product **86** was enantioselectively reduced to the OH group on treatment with alpine borane generated *in situ* (Midland reduction);[47, 115] then the hydroxyl was protected by the methoxymethyl group. This was followed by exhaustive hydrogenation of the triple bond of alkyne **87** with diamide obtained *in situ* in the reaction of tosylhydrazine

Scheme 25



9-BBN is 9-borabicyclo[3.3.1]nonane

Scheme 26



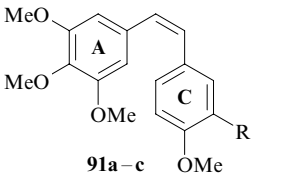
and sodium acetate in a monoglyme – water mixture.[116] Palladium-catalyzed methoxycarbonylation of hydrogenation product **88** with the methanol – carbon monoxide system completed the formation of substrate **89** for the key cyclization step.

The intramolecular CH-arylation of aryl chloride **89** leading to tricyclic product **90** proceeded with a good yield at 145 °C in dimethylacetamide (DMA) in the presence of the palladium acetate – DavePhos Buchwald ligand – potassium carbonate catalytic system (Scheme 26).[117] The authors noted that the selection of the optimal ratio of the precatalyst and the ligand (equimolar amounts) allowed them to reduce the amount of the by-product resulting from hydrodehalogenation of aryl chloride **89**. After cyclization, the methoxymethyl protecting group was removed by treatment with a solution of HCl in aqueous ethanol. The subsequent transformations of the functional group at C(7), particularly, the Mitsunobu (S_N2) substitution of an azide group for the hydroxy group,[47] hydrogenation of the azide with lithium aluminium hydride and acetylation of the resulting amine with acetic anhydride in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP), furnished the target (−)-allocolchicine (**2**) in a 21% overall yield (11 steps) and 98% *ee*.

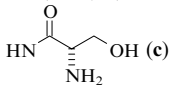
The same strategy was used to prepare an allocolchicine analogue devoid of the ester group in ring **C**.

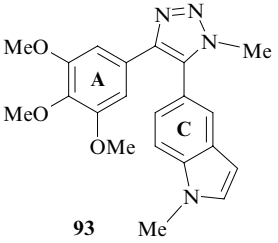
VI. Methods for the synthesis of hetaryl-containing allocolchicinoids

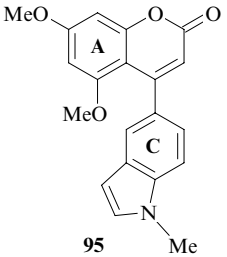
A recent trend is to prepare analogues of the colchicine site ligands containing no tricyclic fused system (for example, *Z*-stilbenes **91**)[118 – 124] and containing heteroaromatic rings (for example, 4-arylcoumarins **92**).[125 – 128] The key structural characteristics of these derivatives is the presence of two non-coplanar polymethoxy- and/or polyhydroxy-substituted *syn*-aryl moieties **A** and **C** located at a definite distance from each other.[128] The replacement of 3-hydroxy-4-methoxyphenyl moiety (**C**) in combretastatin (**91a**) by the 1*H*-indole moiety with simultaneous modification of the linker between the pharmacophore groups **A** and **C** gave rise to a number of compounds **93** with high biological activity.[129] Trimethoxybenzoylindoles, -benzo[*b*]furans and -benzo[*b*]thiophenes **94** effectively inhibit tumour cell proliferation and tubulin polymerization by interacting with the colchicine site of tubulin.[130 – 135] 4-Hetarylcoumarin **95** containing the 1-methyl-1*H*-indol-5-yl pharmacophore moiety inhibits proliferation of HBL 100 breast cancer cells when present in nanomolar concentrations (IC_{50} = 73 nmol litre^{-1}).[136] The geometric parameters of **95** (torsion angle and distance between the centres of rings **A** and **C**) were determined by X-ray diffraction. This compound was found to be a close structural analogue of combretastatin A-4 (**91a**).

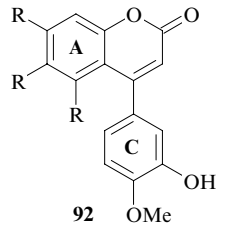


R = OH (**a**, combretastatin A-4),
$OPO(ONa)_2$ (**b**, CA4P),

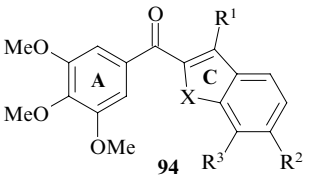






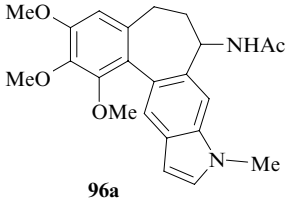


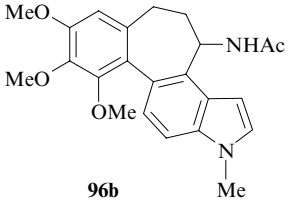
R = H, OMe



X = NH, NMe, O, S;
R^1 = Me, Ar, NH_2, NMe_2, NHAr;
R^2 = H, OMe, OEt;
R^3 = H, OMe

In 2012, the first hetaryl allocolchicinoids **96a**,**b** were synthesized.[33]

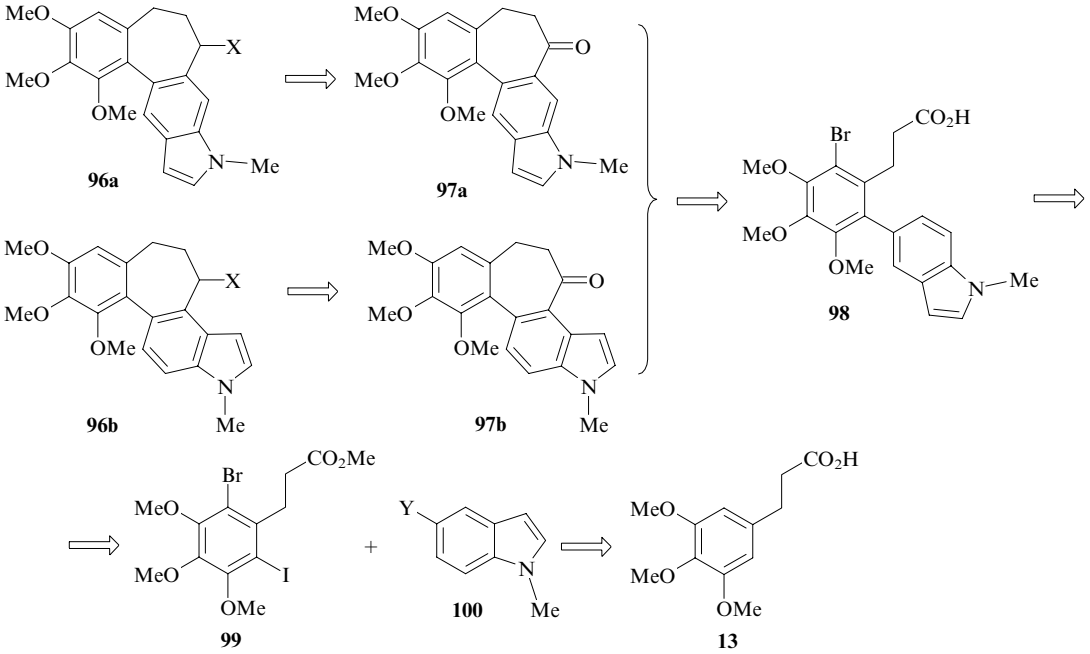




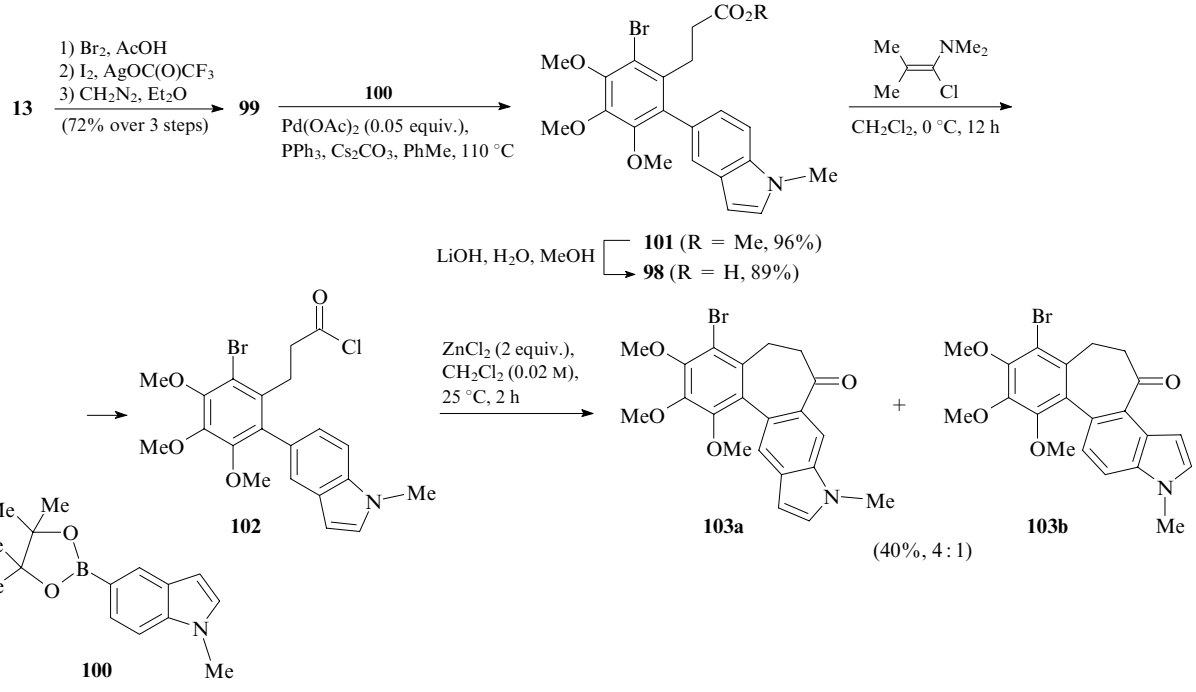
The key intermediates for the synthesis of indoloallocolchicines **96a**,**b** are tetracyclic ketones **97a**,**b** (retrosynthetic analysis is presented in Scheme 27), which can then serve as substrates for the preparation of derivatives with various functional groups at C(7). A suitable route for the formation of the seven-membered ring in these compound is the intramolecular Friedel–Crafts acylation of compound **98**. The bromine atom in biaryl **98** serves as a protecting group, which prevents an electrophilic attack at the electron-saturated trimethoxyphenyl moiety (Scheme 27) and can be removed after cyclization by reductive dehalogenation.[137] For preparing derivative **98**, it was proposed to use catalytic cross-coupling of aryl iodide **99** and organoboron derivative **100**. Aryl halide **99**, in turn, is a derivative of the already mentioned 3-(3,4,5-trimethoxyphenyl)propionic acid (**13**).

The synthesis was started with the transformation of acid **13** into dihalo-substituted ester **99** by bromination, iodination with the iodine–silver trifluoroacetate system and esterification with diazomethane (Scheme 28). The overall yield over three steps was 72%. This was followed by the Suzuki–Miyaura reaction of aryl halide **99** and 1-methyl-1*H*-indol-5-ylboronic acid pinacolate (**100**) in boiling toluene in the presence of the palladium acetate–triphenylphosphine–caesium carbonate catalytic system, which produced the target product **101** in 96% yield (see Scheme 28). Attempts[138,139] to cyclize ester **101** under the action of Lewis acids (aluminium chloride, boron

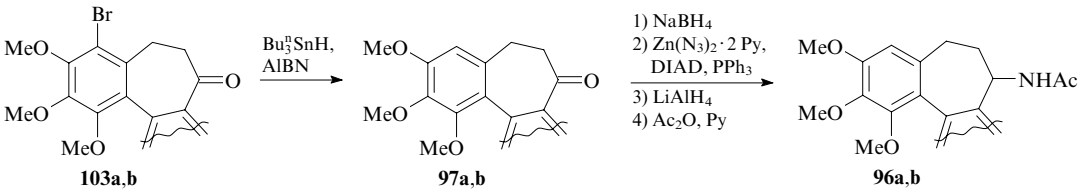
Scheme 27



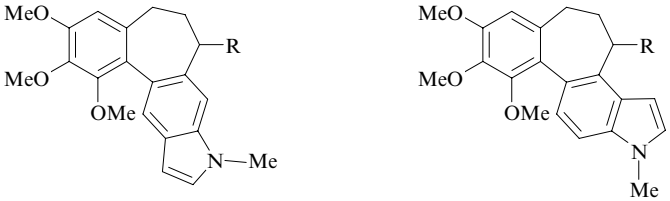
Scheme 28



Scheme 29



Compound	Yield (%)	Compound	Yield (%)
104a	92	**104b**	93
105a	89	**105b**	68
96a	87	**96b**	89



rac-**104a**, **105a**, **96a** *rac*-**104b**, **105b**, **96b**

R = OH (**104a**,**b**), N_3 (**105a**,**b**), NHAc (**96a**,**b**)

trifluoride etherate, zinc chloride) and polyphosphoric acid furnished complex mixtures of products as a result of side alkylation. The corresponding carboxylic acid **98** also did not cyclize on treatment with polyphosphoric acid or catalytic amounts of scandium(III) triflate.[140] The difficulty of conducting the intramolecular Friedel – Crafts reaction with derivatives **98** and **101** is due to the fact that indole and its derivatives are highly prone to oligomerization in acidic solutions or in the presence of strong Lewis acids.[141, 142] It was found that conversion of acid **98** to chloride **102** can be accomplished by treatment with dimethyl(1-chloro-2-methylpropenyl)amine (see Scheme 28). This reagent, which is an analogue of the formylating species in the Vilsmeier – Haack reaction, was proposed for the first time by Ghosez and co-workers.[143] Chloride **102** underwent *in situ* intramolecular Friedel – Crafts acylation in the presence of a twofold excess of zinc chloride, which gave regioisomers **103a**,**b** in 4 : 1 ratio in 40% overall yield. Other Lewis acids [$AlCl_3$, $ZnBr_2$, $BF_3 \cdot Et_2O$, $Sc(OTf)_3$, $Ti(OPr^i)_4$, $EtAlCl_2$, Et_2AlCl] proved less effective.

The removal of bromine from compounds **103a**,**b** was carried out by reductive dehalogenation in the presence of a radical initiator, azobis(isobutyronitrile) (AIBN), which produced a mixture of isomeric ketones **97a**,**b** (Scheme 29). The isomers were separated by chromatography on silica gel with addition of potassium fluoride (9 : 1).[144] The yield of products **97a**,**b** was 92% and 90%, respectively.

Further transformation of the carbonyl group of compounds **97a**,**b** into an acetamide group was performed in 4 steps (see Scheme 29).[26] First, ketones **97a**,**b** were reduced with sodium borohydride to alcohols *rac*-**104a**,**b**. Then the hydroxy group was replaced by an azide group *via* S_N2 mechanism on treatment with zinc azide in the presence of diisopropylazidicarboxylate and triphenylphosphine (Mitsunobu reaction). The reduction of the azide group in **105a**,**b** with lithium aluminium hydride and acetylation of the amines thus formed afforded the desired acetamides *rac*-**96a**,**b** in 87% and 89% yields over two steps. Thus, allocolchicinoids *rac*-**96a**,**b** were prepared from commercially available acid **13** in 11 steps in overall yields of 14% and 3%, respectively.

Allocolchicinoids **104**, **105**, and **96** were isolated as mixtures of atropoisomers (see Section II). Analysis of the ^{1}H NMR spectra demonstrated that these compounds, like allocolchicine (**2**) and *N*-acetylcolchinol (**3**), undergo atropoisomerization in solution at room temperature and the ratio of conformers varies depending on the solvent polarity.[33]

It was shown that when present in nano- and subnanomolar concentrations, indoloallocolchicinoids **97a**,**b** and **104a**,**b** inhibit cell proliferation and exhibit apoptosis-inducing activity towards lymphoid cells, while having low non-specific toxicity.[33] It was shown that these compounds disrupt the formation in the mitotic spindle and terminate the cell cycle in the G2/M phase.

VII. Conclusion

Allocolchicinoids have been attracting keen attention of synthetic chemists for more than 50 years. Whereas in the earlier stage of development of organic synthesis, allocolchicinoids were prepared from natural colchicine, the main trend of the last 15 years is implementation of total syntheses of the desired molecules from simple commercial substrates. In most of the strategies used in the total syntheses, the key step is annelation to give seven-membered ring **B**, which may be performed both using classical approaches of organic chemistry (oxidative coupling of two aromatic moieties, condensation and Friedel – Crafts reactions, the Nicholas reaction) and using modern metal complex catalysis techniques (ring closure metathesis, catalytic CH-activation). Also two methods were proposed that imply the attachment of ring **C** to the **AB** system using the Diels – Alder or Dötz reactions. Finally, an elegant approach to the design of the 6,7,6-tricyclic allocolchicinoid molecular skeleton is the ring **B** expansion in phenanthrol substrate **47** *via* intermediate cyclopropanation.

Note that the Windaus method, which was proposed in the early 1950s and recently upgraded, provides enantioselective synthesis of allocolchicinoids starting from natural colchicine with the use of short, non-laborious and inexpensive sequences of reactions, which is obviously an important advantage over the described total syntheses. Nevertheless, total syntheses enable the preparation of wide ranges of intermediates and building blocks for the compilation of new libraries of allocolchicinoids. Allocolchicinoids, which have simpler structures than taxanes, epothilones, colchicine and other tubulin ligands, are of considerable interest for biomedical chemistry.

From the fundamental standpoint, an equally important advantage of some multistep syntheses over the Windaus method is, in our opinion, the potential way for controlling

the axial configurations of some substituted allocolchicinoids (see, for example, preparation of compound **69**). A basic question has not been answered to date, particularly, what is the axial configuration of the biologically active conformers of allocolchicine and its analogues? Perhaps, it is the combination of the unique conformational mobility and the structure of allocolchicinoids (positions of the pharmacophore groups, the size of the molecule, *etc*.) that is responsible for the outstanding antitumour properties of this class of compounds. Indeed, a molecule of the proper structure and size subject to some atropoisomerization will evidently interact more readily with the colchicine site of the intracellular protein tubulin. In our opinion, a promising trend in the development of the allocolchicinoid chemistry is related to the synthesis of derivatives with adjustable conformational mobility, study of the conformational dynamics [25, 35] and correlation of these characteristics with the biological properties of the resulting molecules.

The unique antitumour activity found for the first heterocyclic allocolchicinoids, pyrroloallocolchicinoids,[33] which were synthesized in 2012, implies that the synthesis of hetaryl-substituted derivatives may be considered as one more avenue of the development of this field of chemistry. One may expect that in the near future, allocolchicinoids would remain important target products of fine organic synthesis.

This review was written with the support from the Russian Foundation for Basic Research (Project No. 12-03-00214-a) and the Federal Target Programme 'Scientific and Scientific-Pedagogical Personnel of Innovative Russia' in 2009 – 2013 (contract No. 16.740.11.0476).

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