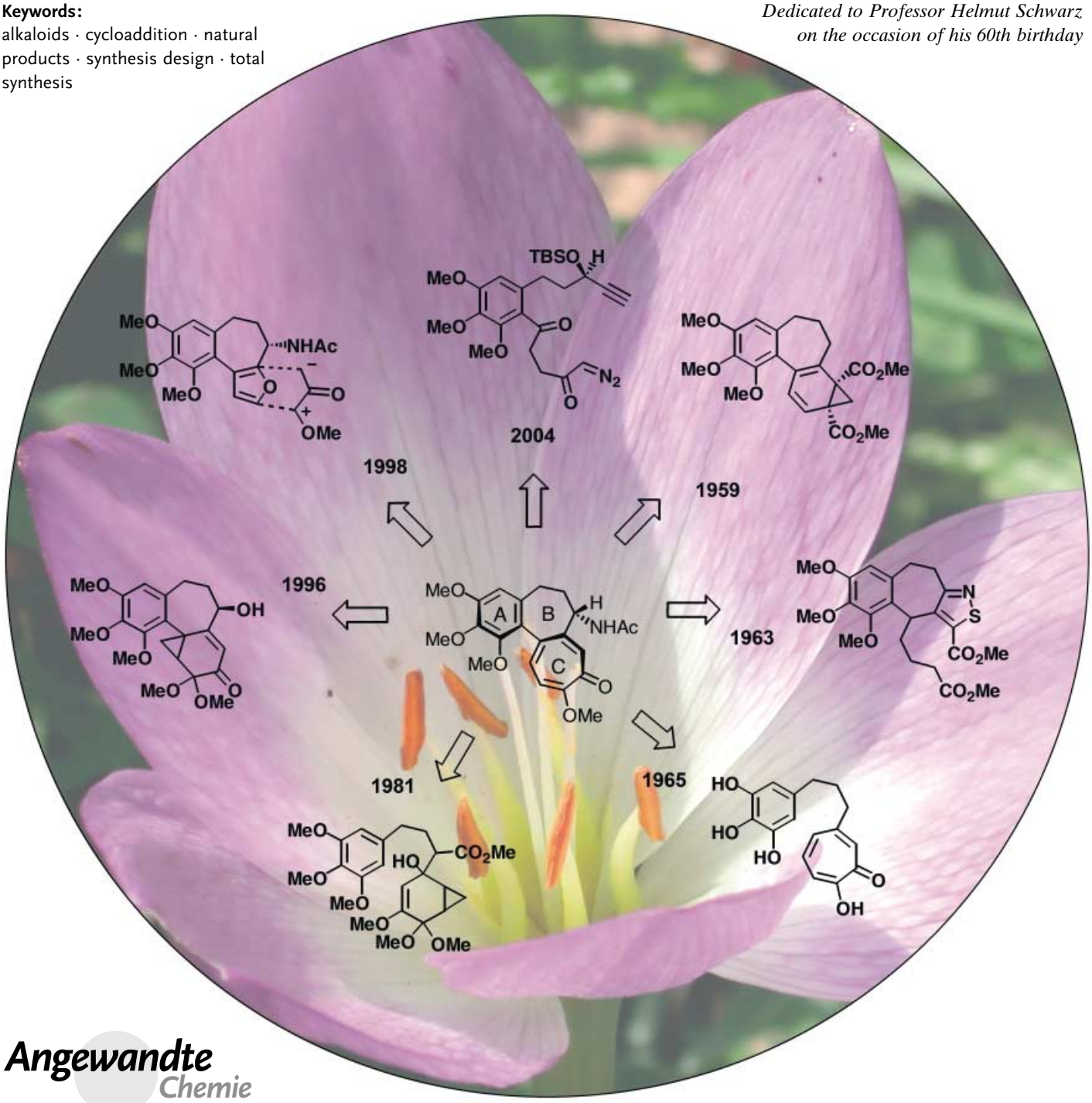
Natural Products Synthesis

# Total Syntheses of Colchicine in Comparison: A Journey through 50 Years of Synthetic Organic Chemistry

*Timm Graening and Hans-Günther Schmalz**

**Keywords:**
alkaloids · cycloaddition · natural products · synthesis design · total synthesis

*Dedicated to Professor Helmut Schwarz on the occasion of his 60th birthday*



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*Colchicine, the major alkaloid of the meadow saffron, is one of the most prominent natural products and, like other tubulin-binding natural products (e.g. taxol and the epothilones), exhibits great pharmaceutical potential. The first syntheses in the late 1950s were milestones in natural product synthesis. But even today this structurally supposedly simple molecule poses a challenge to synthetic chemists. Only in the last years have syntheses been developed that are efficient enough to provide novel structurally modified colchicine analogues. The comparative examination of all known colchicine total syntheses undertaken in this Review not only reveals the tremendous progress in synthetic organic methodology over the past decades, but also shows how the unique synthetic problems posed by this molecule can be solved in an exceptionally creative manner. Only a few target molecules have been synthesized in such multifaceted ways.*

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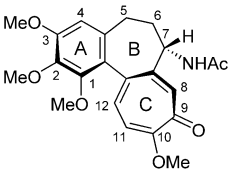
## 1. Structure Elucidation and Biosynthesis

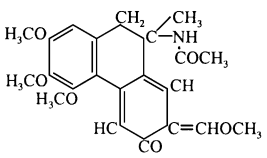
Colchicine (**1**) is the main alkaloid of the poisonous plant meadow saffron (*Colchicum autumnale* L.),[1] a common plant of European and North African origin that flowers in autumn on a leafless stalk (Figure 1). Despite its alternative name, autumn crocus, it belongs to the family Liliaceae.



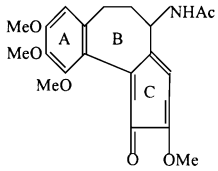

**1** (–)-(a*R*,7*S*)-colchicine

The name *Colchicum* is derived from Colchis, a region east of the Black Sea that is known in Greek mythology as the home of the Golden Fleece and the notorious poisoner Medea. Besides their use as a poison, the active ingredients of the *Colchicum* species belong to the oldest known drugs and have been used for more than 2000 years in the treatment of acute gout.[2]

Colchicine (**1**) was first isolated in 1820 by Pelletier and Caventou,[3] the same natural scientists who had previously isolated the important natural products strychnine, brucine, and quinine. Several aspects of this unusual alkaloid have challenged chemists in the past. In fact, the elucidation of the chemical structure and the biosynthesis of colchicine represent historic achievements in natural product chemistry. Despite considerable efforts, the structure remained uncertain for a long time. After investigations by Zeisel (1883–1913), which led to the development of a method for the determination of methoxy groups,[4] Windaus (1910–1924) made some more specific structural proposals, which were erroneously based on a phenanthrene ring system (**2**).[5]




**2** (Windaus, 1924)




**3** (Dewar, 1945)

The key to the elucidation of the colchicine structure was the correct interpretation of the experimental data concerning ring C of the tricyclic skeleton. Significant progress was made by Dewar in 1945, who assumed that ring C was a cycloheptatrienolone with aromatic character (**3**).[6a] Together with his structural proposal for stipitatic acid in the same year, this hypothesis marked the starting point of the chemistry of tropolones, the term coined by Dewar for this class of compounds.[6b] The correct structure of colchicine was confirmed in 1952 by means of X-ray crystal-structure analysis,[7]


***Figure 1.*** Meadow saffron (*colchicum autumnale* L.).[1f]

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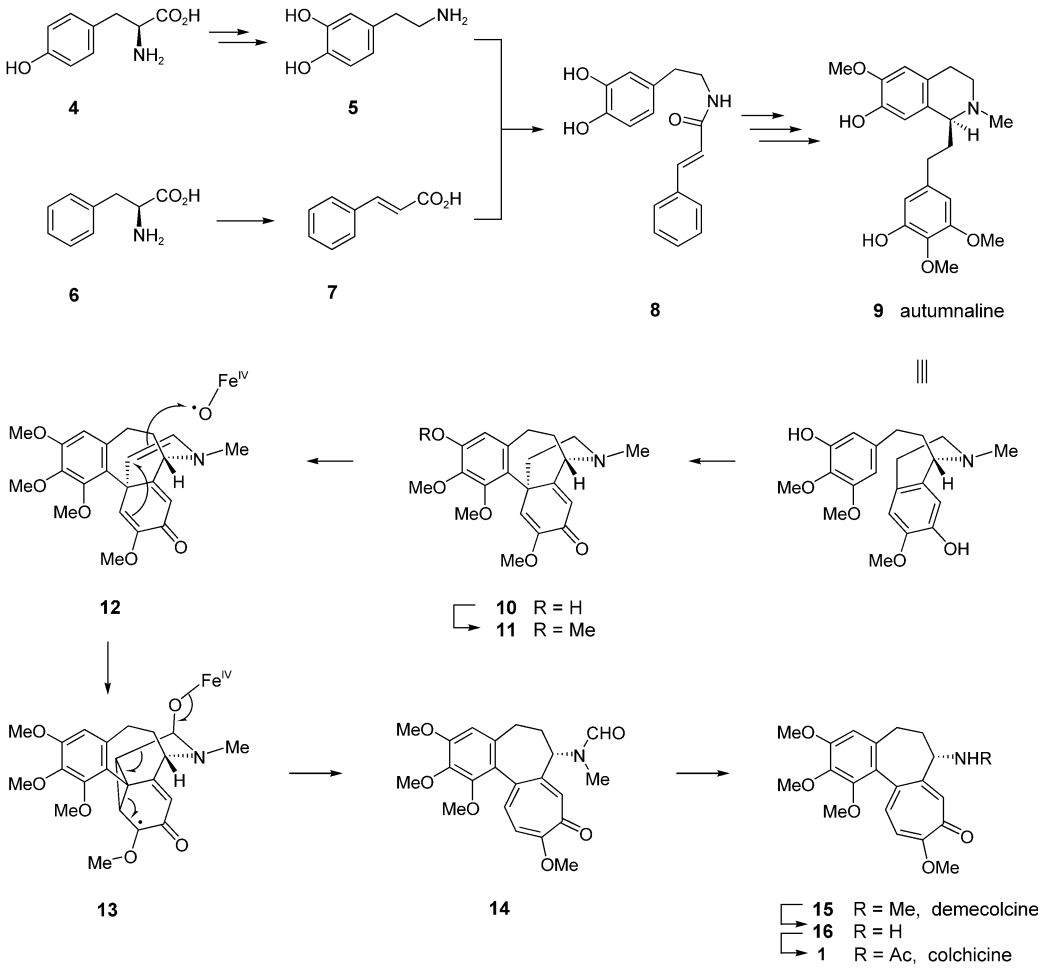


***Scheme 1.*** Colchicine biosynthesis.

and the absolute configuration was proven by chemical degradation.[8]

The biosynthesis of colchicine was puzzling in the beginning, because the unusual ring system did not show any clear relationship to other types of plant alkaloids. Many different hypotheses were put forward before the groups of Leete and, in particular, Battersby proposed the currently accepted biosynthetic route based on a large number of labeling and incorporation experiments.[9] This pathway involves a *para*/*para* phenol coupling of autumnaline (**9**, Scheme 1).

The cyclization product **10** is then methylated and dehydrogenated enzymatically to the enamine **12**, before a subsequent skeletal rearrangement takes place to form the tropolone ring. It is assumed that this process (**12**→**13**→**14**) is triggered by a cytochrome P450-dependent oxidation. The final steps involve deformylation to give demecolcine (**15**), followed by demethylation and acetylation to give colchicine (**1**).

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*Timm Graening, born in 1971 in Flensburg (Germany), studied chemistry at the Christian-Albrechts-Universität Kiel and joined the group of Prof. Schmalz at the University of Cologne in 2000. In his doctoral thesis he is currently working on the total synthesis of colchicine.*

## 2. The Colchicine/Tubulin Interaction

Colchicine (**1**) is an important bioactive compound used in the treatment of a broad variety of diseases and still remains the sole drug for the therapy of acute gout and familial Mediterranean fever.[10] Moreover, colchicine acts as an antimitotic agent by binding to tubulin (Figure 2). Tubulin is

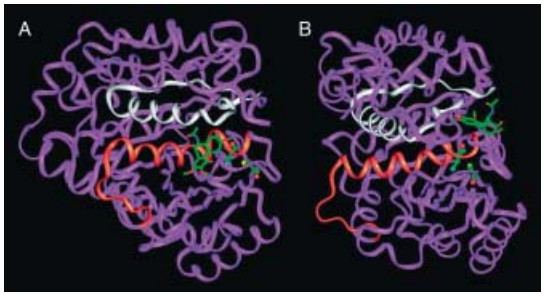



***Figure 2.*** Electron crystallographic structure of the αβ-tubulin dimer with two alternative binding modes for colchicine (A and B) as found by molecular modeling.[18]

a globular protein and was formerly known as colchicine-binding protein.[11] In the presence of guanosine triphosphate (GTP), tubulin forms heterodimers consisting of an α and a β subunit. These α,β-dimers assemble in a helical fashion into polymeric tubes, the so-called microtubules (Figure 3).[12]

***Figure 3.*** Model for the assembly of αβ-tubulin dimers to microtubules.

These long protein fibers, which consist of 12 to 13 protofilaments with an alternating linear arrangement of α- and β-tubulin units, exist in dynamic equilibrium with the tubulin dimer. Microtubules are polar structures with a faster-growing (+) and a less-dynamic (−) terminus. They have an outer diameter of 24 nm and form a hollow cylinder with a diameter of approximately 15 nm. The microtubules are responsible for several important functions within the cell: Besides mechanically stabilizing cellular structures, they serve as "highways" for transport and signal processes. Most importantly, however, they form the mitotic spindle during cell division (Figure 4).

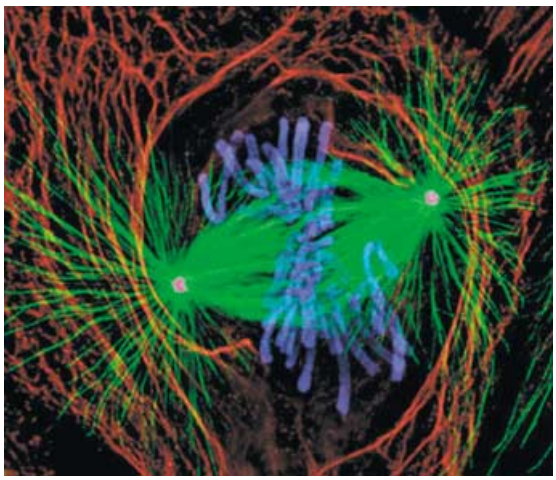
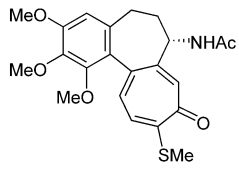


***Figure 4.*** Fluorescence microscopy image of the spindle apparatus of a cell during the process of mitosis in the metaphase. The microtubules are marked green and the chromosomes are colored blue.

At this point colchicine exerts its dramatic effect: By binding to the tubulin dimer, it distorts the tubulin/microtubule equilibrium in such a manner that mitosis is arrested in the metaphase. In fact, several so-called spindle poisons exert their influence at this very stage, making this a very successful approach for cancer chemotherapy. Whereas colchicine and vinblastine induce depolymerization of microtubules, other drugs such as taxol and the epothilones effect their stabilization.[13] Therefore such compounds can be used to selectively damage the rapidly proliferating cancer cells. However, the general toxicity of colchicine has hampered its use in cancer chemotherapy so far. A large number of colchicine analogues have been prepared in the past from the natural product itself, with the aim of developing new antitumor agents, and some QSAR (quantitative structure–activity relationship) studies have been performed.[14] Nevertheless, the general toxicity could hardly be suppressed. For example, thiocolchicine (**17**)[15] and demecolcine (**15**),[16] which show a comparable activity and enjoy medical application, exhibit a slightly lower toxicity.




**17** thiocolchicine

As a result of the success of taxol in the treatment of mammalian and ovarian cancer, molecules that interact with the colchicine-binding site of tubulin have regained pharmaceutical interest. According to the National Cancer Institute, they are considered as important lead structures for the development of new antitumor agents.[17] So far, a major obstacle in the identification of more-active colchicine derivatives was the difficulty in accessing colchicine and its structural analogues by means of total synthesis. Also, the rational design of new colchicine-related drugs is

complicated by the fact that the binding site and the mechanism leading to the destabilization of microtubules are not yet fully understood.[18] Unquestionably, colchicine binds in a temperature-dependent and irreversible manner to a high-affinity binding site at the β-tubulin subunit, inducing a partial unfolding at the carboxy terminus.[19] It is assumed that this change in the secondary structure affects the regions of the protein dimer that are essential for microtubule formation. Different opinions have been put forward concerning the conformational changes of colchicine itself during its interaction with the protein.[20] Nevertheless, it has been clearly demonstrated that the helical twist inherent to the colchicine ring skeleton, seems to be of prime importance for effective binding. The molecule contains a stereocenter at C7 as well as an a*R*-configured chiral axis defined by the pivot bond joining rings A and C (Figure 5).[21] Berg et al. were able

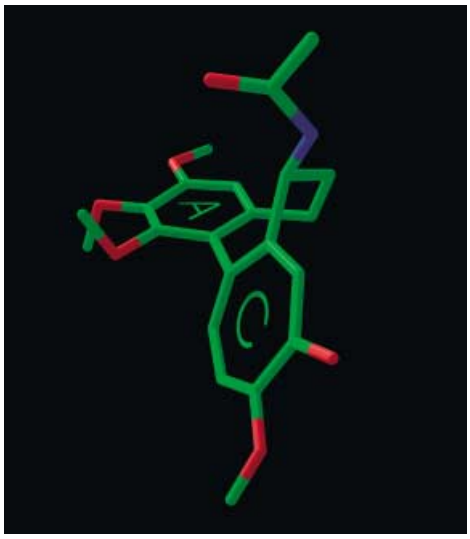
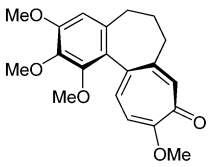
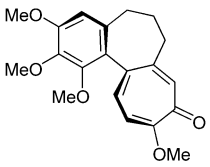



***Figure 5.*** Stereostructure of colchicine.

to separate the atropisomers of desacetamidocolchicine (a*R*-**18**, a*S*-**18**) and were able to demonstrate that only the a*R* enantiomer binds to tubulin.[22]



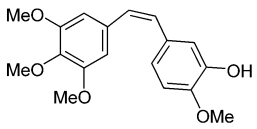

a*R*-**18**




a*S*-**18**

During the search for new drugs, a series of compounds were discovered by chance which also interact with the colchicine-binding site of tubulin. Some of them exhibit a great pharmacological potential. Combretastatin A4 (**19**), for instance, is a highly promising antitumor agent which recently passed phase I clinical trials.[23]

To study the interaction of colchicine analogues with tubulin in more detail, an efficient and flexible total synthetic

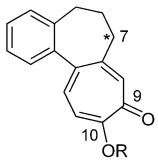



**19** combretastatin A4

access would be required. A deeper understanding of the complex phenomena could ultimately lead to a rational design of new drugs derived from colchicine as a lead structure.

## 3. Target Structure and Classification of the Total Syntheses

In the 1950s, colchicine was considered as a milestone in natural product synthesis, and the first syntheses from the laboratories of Eschenmoser and van Tamelen in 1959 were highly recognized masterpieces of synthetic chemistry,[24–26] a field that was rapidly developing at this time. By today's standards of synthetic chemistry—highly complex natural products containing novel and often sensitive structural elements are synthesized in the laboratory only a few years after their discovery—the small molecule colchicine (**1**) appears to be a rather simple target at first glance.[27] For that reason, it is remarkable that its synthesis still poses a problem, despite all the modern methodology available. Since the early syntheses of Eschenmoser and co-workers and van Tamelen and co-workers, new approaches towards colchicine have been brought forward continuously, in most cases following fundamentally different strategies.[28–37] However, only in recent years have syntheses been developed that show a satisfying overall efficiency.[38–40] The reason for the difficulties inherent to the target structure does not result from a lack of general methods for the synthesis of tropolones. Also, stereocontrol does not pose too much of a problem, because the configuration of the chiral axis is thermodynamically predetermined by the stereogenic center at C7. The main difficulty actually lies in the regioselective construction of the highly oxidized ring C within the unusual 6,7,7-membered ring system **20**.



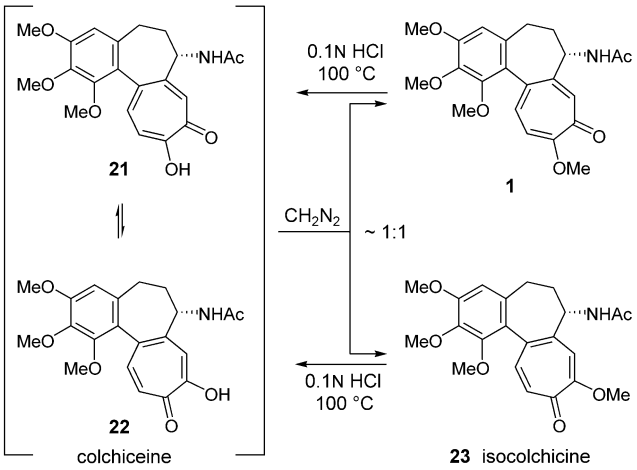

**20**

The tropolone ring C is deeply embedded within the molecular architecture by the neighborhood of the stereocenter, the direct connection to the benzenoid ring, and its annulation to the seven-membered ring B. Therefore, its generation forms an integral part of any synthetic strategy. During many investigations directed towards the total synthesis of colchicine, it became clear that in this context standard methods for tropolone formation either gave bad yields or were complicated by regioselectivity problems. Also the introduction of tropolone derivatives as ring C building blocks has hitherto been disadvantageous.[30,32,33,41] Thus, specific methodology for the construction of annulated tropolones is a precondition for any efficient total synthesis.

The chemistry of the parent tropolone and simple tropone and tropolone derivatives has been studied extensively since the 1950s.[42] Tropolones exist in a tautomeric equilibrium and behave similarly to phenols with respect to aromatic substitution. Their acidity ($pK_a = 7$) is inbetween those of phenols and carboxylic acids. The carbonyl group shows little ketone character and should rather be considered as part of a vinylogous carboxylic acid. The aromatic character of tropolone, which was a matter of intense debate in the past, should not be overemphasized.

The free tropolone derived from **1** is named colchiceine. It is a prominent colchicine precursor, which exists in a tautomeric equilibrium (**21**/**22**) and can be easily converted into colchicine by treatment with diazomethane (Scheme 2).



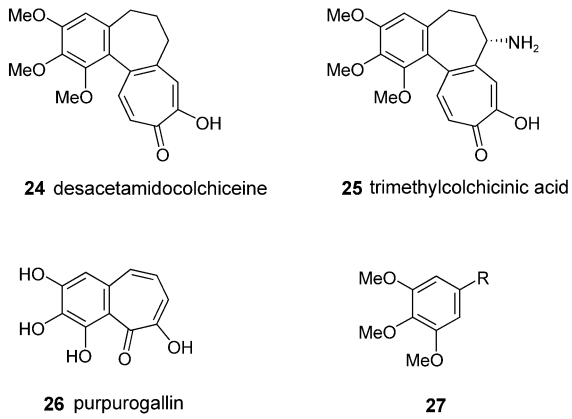

***Scheme 2.*** Interconversion of colchiceine (**22**), colchicine (**1**), and isocolchicine (**23**).

Actually, a 1:1 mixture of colchicine (**1**) and isocolchicine (**23**) is formed, which can be separated by chromatography. The undesired isomer can then be recycled by cleavage of the methyl ether upon heating with dilute hydrochloric acid.[43]

Besides colchiceine (**21**/**22**), other important intermediate molecules that have been reached in formal total syntheses are desacetamidocolchiceine (**24**) and the advanced colchicine precursor trimethylcolchicinic acid (**25**), both of which had been converted into the target compound **1** during the early syntheses (Scheme 3). As a readily available starting material, purpurogallin (**26**) was used in several syntheses, and the majority of the other syntheses started from a symmetric C5-substituted pyrogallol trimethyl ether of type **27**.

To give an overview of the various synthetic approaches towards colchicine, including formal total syntheses, it is advantageous to classify them according to the cyclization strategies used in the construction of the 6,7,7-membered ring system (Scheme 4).

Monotopic cyclization strategies involving the formation of strategic bonds in ring B or C (AC→ABC or AB→ABC, respectively) make up the majority of the early syntheses. In these systems, however, the crucial ring-closing reactions




***Scheme 3.*** Important colchicine intermediates and starting materials.

proceed with only low to moderate yields. A second major group encompasses strategies that exploit five- or six-membered cyclic precursors for the construction of the crucial tropolone ring C (ABC′→ABC, AB′C′→ABC, AC′→ABC). A common feature of most of these syntheses is the preparation of the seven-membered ring by a ring enlargement of a norcarane precursor. Following this concept, some fascinating transformations for the construction of ring C in a highly oxidized form, or even as the complete tropolone ring, have been designed. The greatest retrosynthetic simplification of the fundamental *ortho*-condensed ring system corresponds to an intramolecular cycloaddition strategy (A→ABC). Ideally, both seven-membered rings B and C are formed simultaneously with the correct placement of the oxygen functions in ring C.

The different strategies developed for the total synthesis of **1** in the course of the past 50 years are presented in the following sections, with an emphasis on the overall synthetic scheme.[44] The order of the syntheses is not strictly chronological. Instead, the conceptually different synthetic routes are organized according to the progress that they contributed to the solution of key synthetic problems.

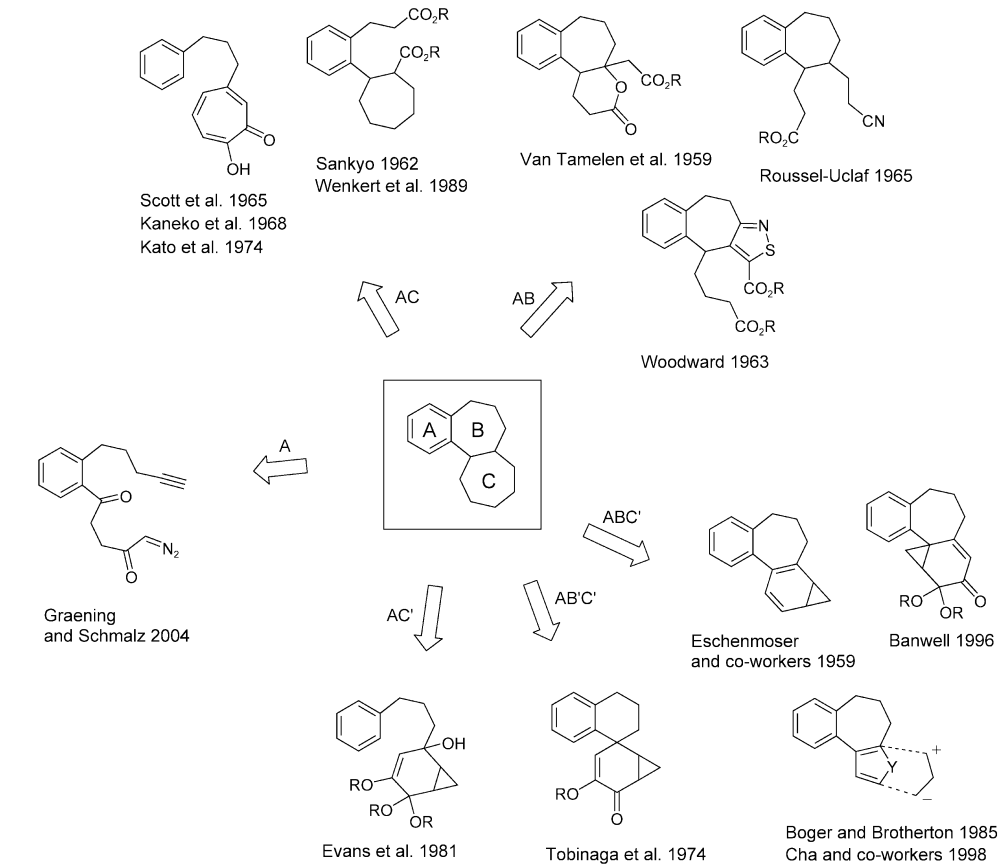
## 4. Colchicine Total Syntheses

### 4.1. The Scott Synthesis of Desacetamidocolchiceine through Oxidative Coupling

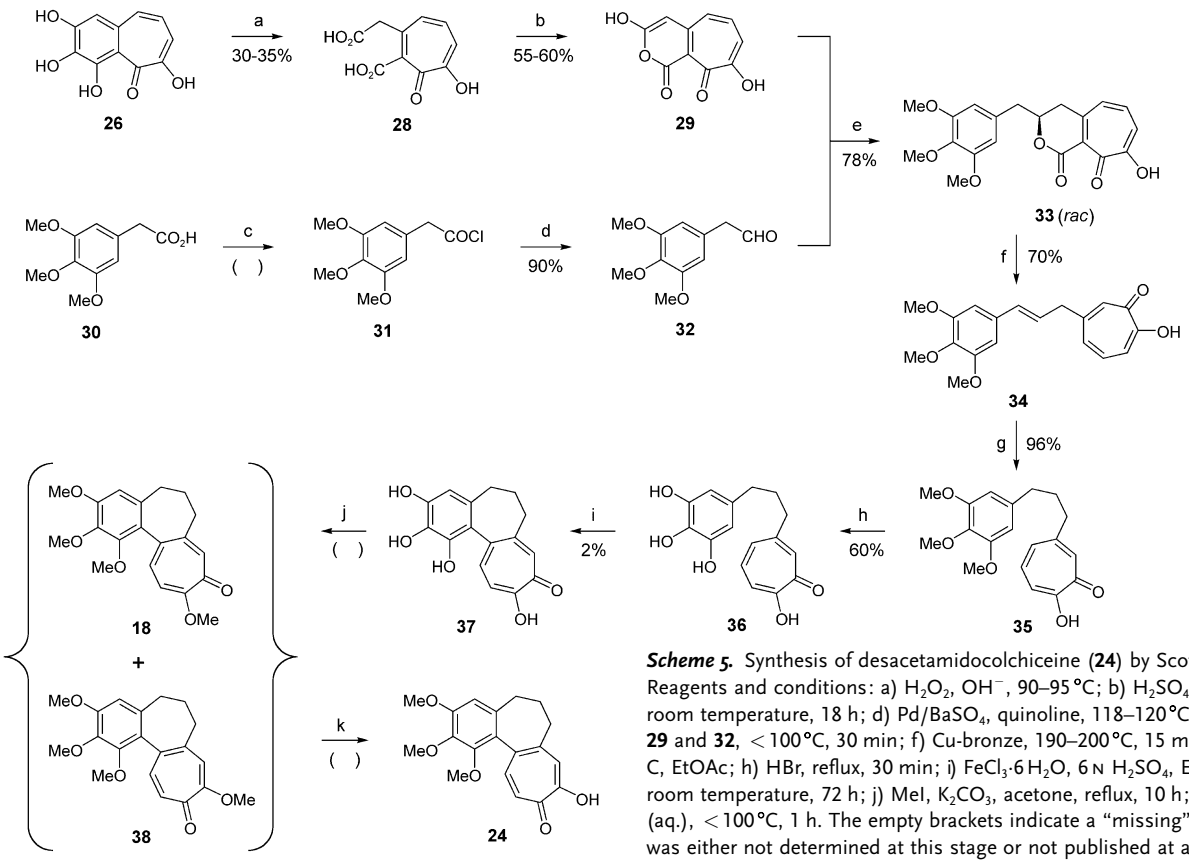
The synthesis reported by Scott et al. in 1965 started from a tropolone derivative as the ring C building block and followed the strategy A + C→AC→ABC (Scheme 5).[30] This synthesis is based on an earlier biosynthetic hypothesis postulating the formation of ring B by oxidative phenol–tropolone coupling.[45]

The tropolone part was derived from purpurogallin (**26**) from which the anhydride **29** was synthesized by oxidative degradation of the electron-rich benzene ring followed by dehydration. By condensation of **29** with the aldehyde **32**, prepared from the acid chloride **30** in a Rosenmund reduction, the lactone *rac*-**33** was obtained under elimination




***Scheme 4.*** Retrosynthetic classification of colchicine syntheses.




***Scheme 5.*** Synthesis of desacetamidocolchiceine (**24**) by Scott et al. Reagents and conditions: a) $H_2O_2$, $OH^-$, 90–95 °C; b) $H_2SO_4$; c) $(COCl)_2$, room temperature, 18 h; d) $Pd/BaSO_4$, quinoline, 118–120 °C, 5 h; e) neat **29** and **32**, < 100 °C, 30 min; f) Cu-bronze, 190–200 °C, 15 min; g) $H_2$, Pd/C, EtOAc; h) HBr, reflux, 30 min; i) $FeCl_3 \cdot 6H_2O$, 6 N $H_2SO_4$, EtOH, $CHCl_3$, room temperature, 72 h; j) MeI, $K_2CO_3$, acetone, reflux, 10 h; k) $H_2SO_4$ (aq.), < 100 °C, 1 h. The empty brackets indicate a "missing" yield, which was either not determined at this stage or not published at all.

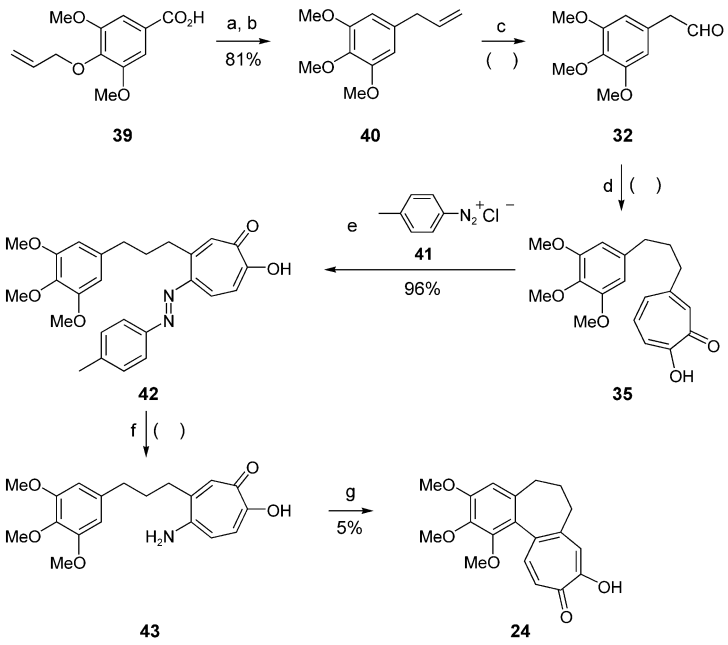
  

of $CO_2$. After elimination/decarboxylation and subsequent hydrogenation of the C–C double bond in **34** (which proceeds smoothly in the presence of the tropolone moiety), the secocolchicine intermediate **35** was obtained in good yield. To prepare for the projected key coupling reaction, the methyl ether groups were cleaved to give the free pyrogallol derivative **36**. Various reaction conditions for the crucial coupling (**36**→**37**) were tested, and it was found that the reaction product was overoxidized under the initially chosen conditions. Eventually, a two-phase oxidation system consisting of $FeCl_3$ in $H_2SO_4$ (6 N) and ethanol in chloroform was used, and the tricyclic product **37** was isolated in 2% yield after preparative paper chromatography under an inert atmosphere. After methylation, the obtained mixture of **18** and **38** was hydrolyzed to desacetamidocolchiceine (**24**), which had been previously converted into (±)-colchicine (*rac*-**1**) by Eschenmoser and co-workers (see Section 4.2.).[25]

Despite the straightforward strategy, the success of the Scott synthesis is diminished by the extremely low yield of the key step. However, the problems associated with this putative biomimetic transformation are in agreement with the fact that the colchicine biosynthesis does not involve a phenol/tropolone coupling, as was recognized later.

#### 4.1.1. The Kaneko Variant of the Scott Synthesis

Kaneko et al. addressed the improvement of the key step in the Scott synthesis. Except for alternative preparation of the aldehyde **32** through decarboxylative Claisen rearrangement and ozonolysis, the seco intermediate **35** was prepared by following the scheme of Scott et al. (Scheme 6).[32]

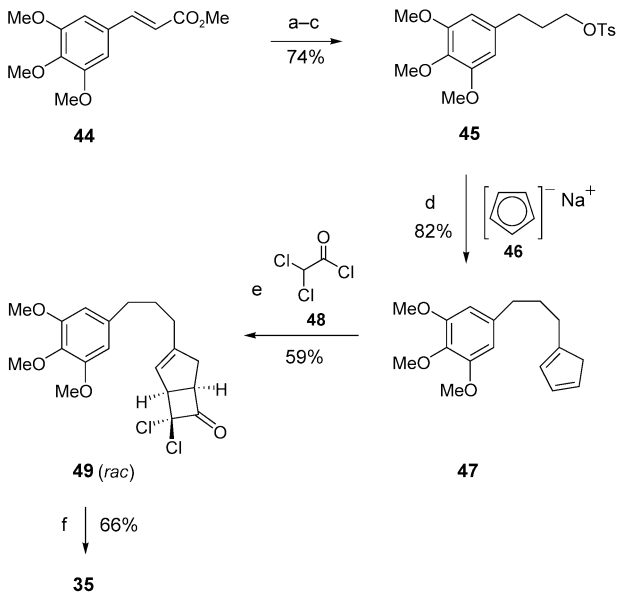



***Scheme 6.*** Synthesis of desacetamidocolchiceine (**24**) by Kaneko et al. Reagents and conditions: a) *N*,*N*-dimethylaniline, reflux, 10 h; b) $Me_2SO_4$, aqueous NaOH, MeOH, reflux, 3 h; c) $O_3$, EtOAc, 30–40 min; then $H_2$, Pd/C, 25 °C; d) reference [30]; e) $NaNO_2$, HCl, $H_2O$, *p*-toluidine, 0 °C (→**41**); then **35**, aqueous NaOH, 2–10 °C, 50 min; f) $H_2$, Pd/C, MeOH, room temperature, 1.5 h; g) isoamylnitrite, conc. $H_2SO_4$, dioxane, 7–10 °C; then Cu powder, dioxane, room temperature, 24 h.

Azo coupling of **35** and subsequent hydrogenation afforded the aminotropolone **43**, which after diazotization directly gave rise to desacetamidocolchiceine (**24**) in a Pschorr cyclization. Unfortunately the yield did not exceed 5%.

#### 4.1.2. The Kato Variant of the Scott Synthesis

An alternative access to the seco intermediate **35** was reported by Kato et al.[33] For the synthesis of the tropolone ring, these authors used the solvolysis of the cyclopentadiene/dichloroketene adduct *rac*-**49** following the Stevens and Bartlett protocol for tropolone synthesis (Scheme 7).[46]

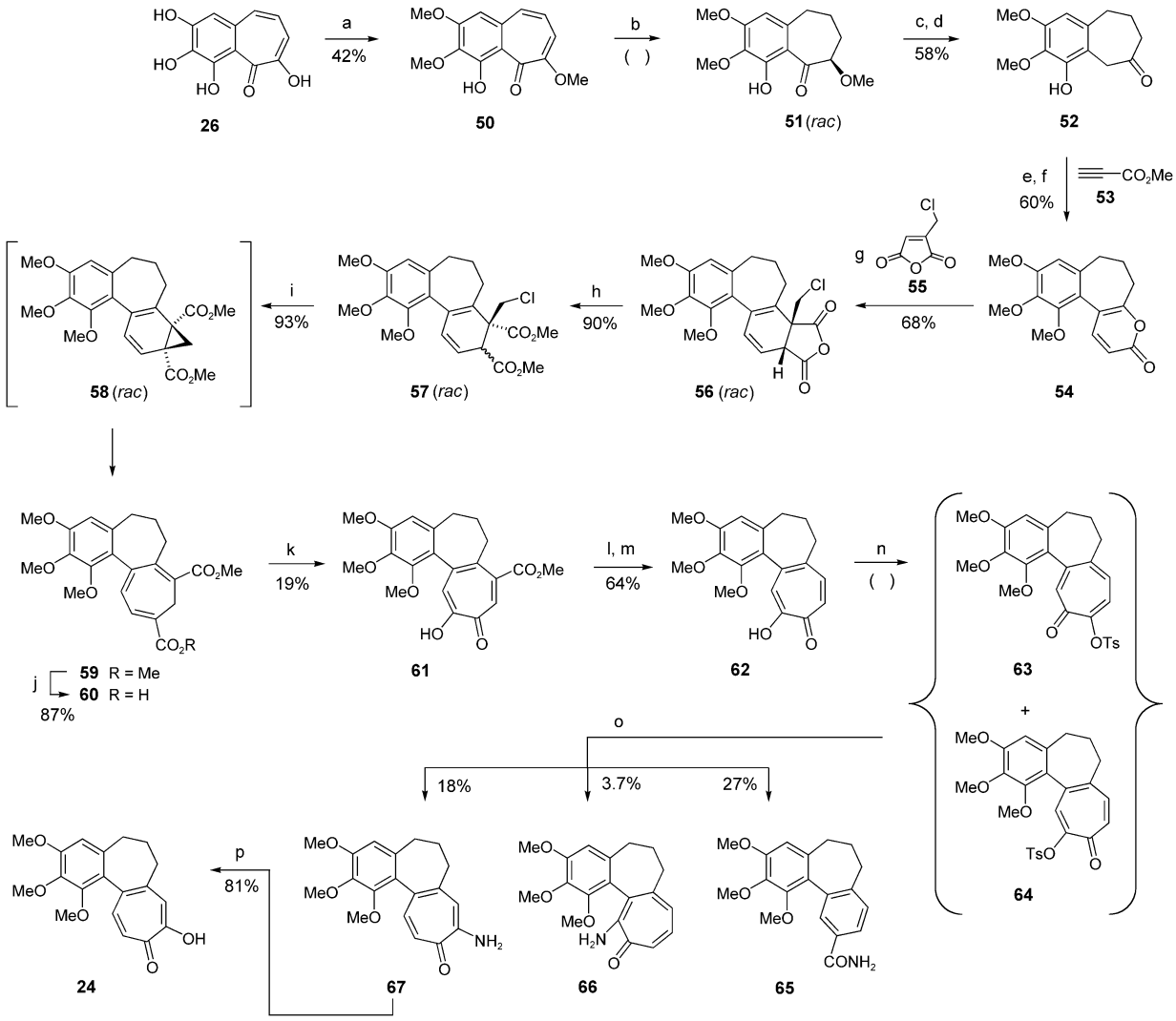



***Scheme 7.*** Synthesis of secodesacetamidocolchiceine (**35**) by Kato et al. Reagents and conditions: a) $H_2$ (1 atm), Pd/C, MeOH, room temperature; b) $LiAlH_4$, $Et_2O$, 0 °C, 4 h, →RT, 14 h; c) TsCl, pyridine, 0 °C, 2 h; d) NaH, cyclopentadiene, THF, 0 °C, then **45**, 3 h; e) **48**, $NEt_3$, *n*-hexane, 5 h; f) KOAc, $H_2O$, HOAc, reflux, 2 days. Ts = *para*-toluenesulfonyl.

The cyclopentadiene precursor **47** was prepared from the tosylate **45** by nucleophilic substitution with sodium cyclopentadienyl (**46**) and concomitant double-bond isomerization. Attempts by Kato et al. to increase the yield of the Pschorr reaction described by Kaneko (**43**→**24**) were not successful.

### 4.2. The Pioneering Eschenmoser Synthesis

The first successful total synthesis of colchicine (**1**), a seminal work by Eschenmoser and co-workers, was reported in 1959.[25] As in the synthesis by Scott et al. discussed before, purpurogallin (**26**) was used as starting material, but in a completely different strategy, that is, as an AB building block (Scheme 8). Therefore, the chosen strategy required

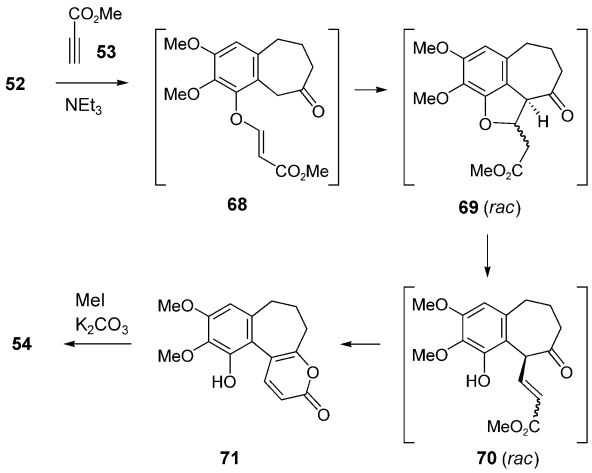


***Scheme 8.*** Synthesis of desacetamidocolchiceine (**24**) by Eschenmoser and co-workers. Reagents and conditions: a) $Me_2SO_4$, NaOH, $H_2O$, 0 °C, 3 h→RT, 7 h; b) $H_2$, Pd, THF, 45 °C, 7.5 h; c) $LiAlH_4$, $Et_2O$, 0 °C, 2.5 h; d) $H_3PO_4$, EtOH, 60–70 °C, 1 h 15 min; e) **53**, $NEt_3$, benzene, *tert*-amylalcohol, reflux, 45 min; f) MeI, $K_2CO_3$, acetone, room temperature, 18 h; g) **55**, 175 °C, 1 h 40 min; h) $H_2SO_4$, MeOH, reflux, 40 min; then $CH_2N_2$; i) KO*t*Bu, *t*BuOH, benzene, room temperature, 2 h 45 min; j) NaOH, $H_2O$, MeOH, reflux, 30 min; k) $OsO_4$, pyridine, $Et_2O$, room temperature, 10 h; then $KClO_3$, $NaHCO_3$, MeOH, 100 °C, 2.5 h; l) NaOH, $H_2O$, reflux, 30 min; m) powdered quartz glass, 260–270 °C, 9 min; n) TsCl, pyridine, room temperature, 14 h; o) $NH_3$, EtOH, 90–95 °C, 15 h; p) aqueous KOH, EtOH, 130 °C, 22 h.

the development of a suitable method for the annulation of the tropolone ring C.

The tropolone ring of trimethylpurpurogallin **50** was reduced, and the product *rac*-**51** was used to prepare the dimethoxybenzosuberone **52**. The free phenol functionality proved to be of importance as several attempts to alkylate the corresponding trimethoxybenzosuberone had failed. As shown in Scheme 9, the free phenol function first undergoes a Michael addition to the electrophilic propyne ester **53** (**52**→**68**). In a second (intramolecular) Michael addition, the tricyclic ketoester *rac*-**69** is formed. Subsequent β elimination of the phenol group and cyclization then leads to the isolated product **71**.

The pyrone **54** obtained after methylation of **71** was then heated with chloromethylmaleic anhydride (**55**) to give the Diels–Alder adduct *rac*-**56** (Scheme 8), which served as starting point for the following key transformation, that is, a



***Scheme 9.*** Intermediates involved in the preparation of the α-pyrone **54** from **52** according to Eschenmoser.

norcaradiene–tropilidene valence tautomerization. Starting from the diester *rac*-**57**, treatment with base led to regioselective formation of the norcaradiene derivative *rac*-**58**, which immediately furnished the tropilidene diester **59** by electrocyclic ring opening. The sterically less-hindered ester group was selectively hydrolyzed, before oxidation with $OsO_4$ afforded the tropolone **61** under decarboxylation. Further decarboxylation gave the product **62**, a regioisomer of the targeted tropolone. The required conversion of **62** into desacetamidocolchiceine (**24**) oxygenated at C9 and C10, relied on the findings of Nozoe et al.[47] Initially, an isomeric mixture of tosylates **63** and **64** was prepared. Ammonolysis then resulted in a tele-substitution, which again afforded a mixture from which the aminotropone **67** was separated and finally converted into desacetamidocolchiceine (**24**) by saponification. This compound was utilized as a relay product, as it could be prepared in four steps from natural colchicine according to a private communication of R. B. Woodward to Albert Eschenmoser (even though at the time Woodward was a competitor in the race for the first synthesis of colchicine).

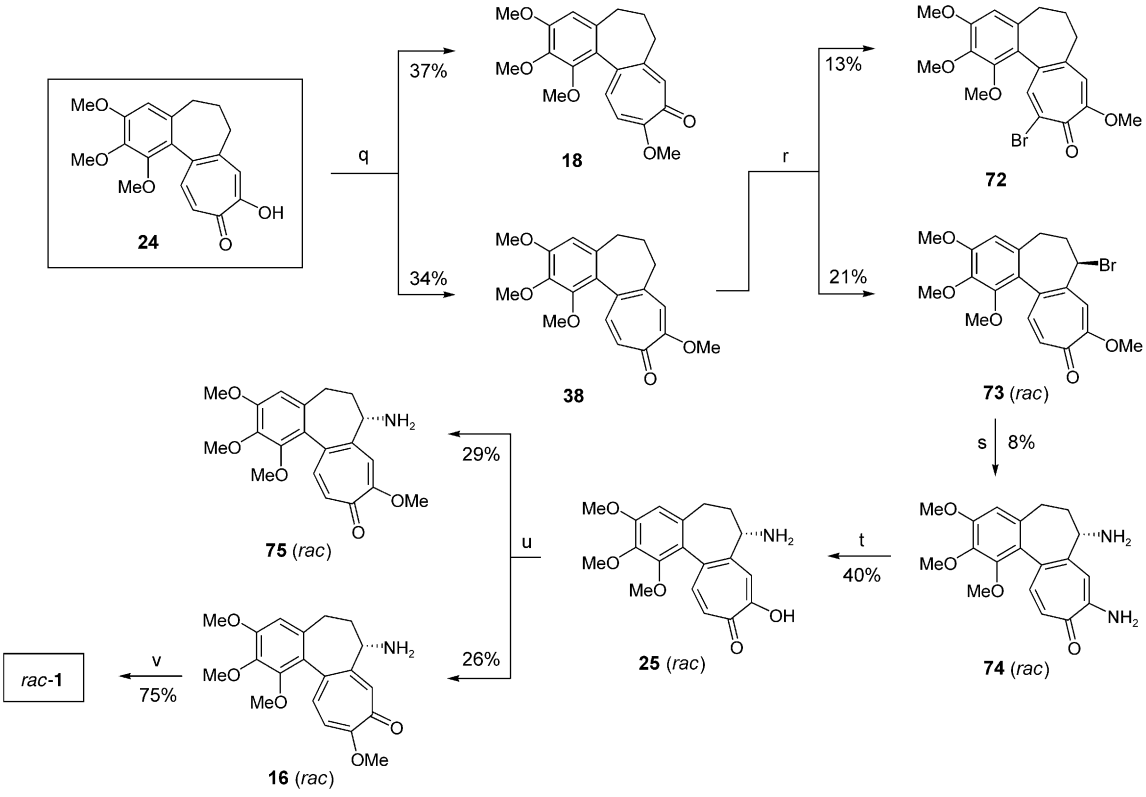
Methylation of **24** led to a mixture of the regioisomers **18** and **38** (Scheme 10). From these regioisomers, only the isocolchicide **38** was a suitable substrate for radical bromination at C7 because of the better stabilization of the radical intermediate. Ammonolysis of the bromination product *rac*-**73** afforded the diamino compound *rac*-**74**, but only in low yield. After remethylation of the hydrolysis product *rac*-**25** and chromatographic separation of the resulting regioisomers, acetylation of *rac*-**16** finally gave racemic colchicine (*rac*-**1**), which had previously been separated into the enantiomers.[48]

The Eschenmoser synthesis opened a highly efficient access to the colchicine ring scaffold with an unsaturated ring C (**59**). In spite of that, the inherent difficulties posed by the target structure became apparent: both the regioselective placement of the oxygen functionalities at C9 and C10 of the tropolone ring and the introduction of the acetamido group at C7 required many additional steps and proceeded with rather low yield and selectivity.

### 4.3. The van Tamelen Synthesis

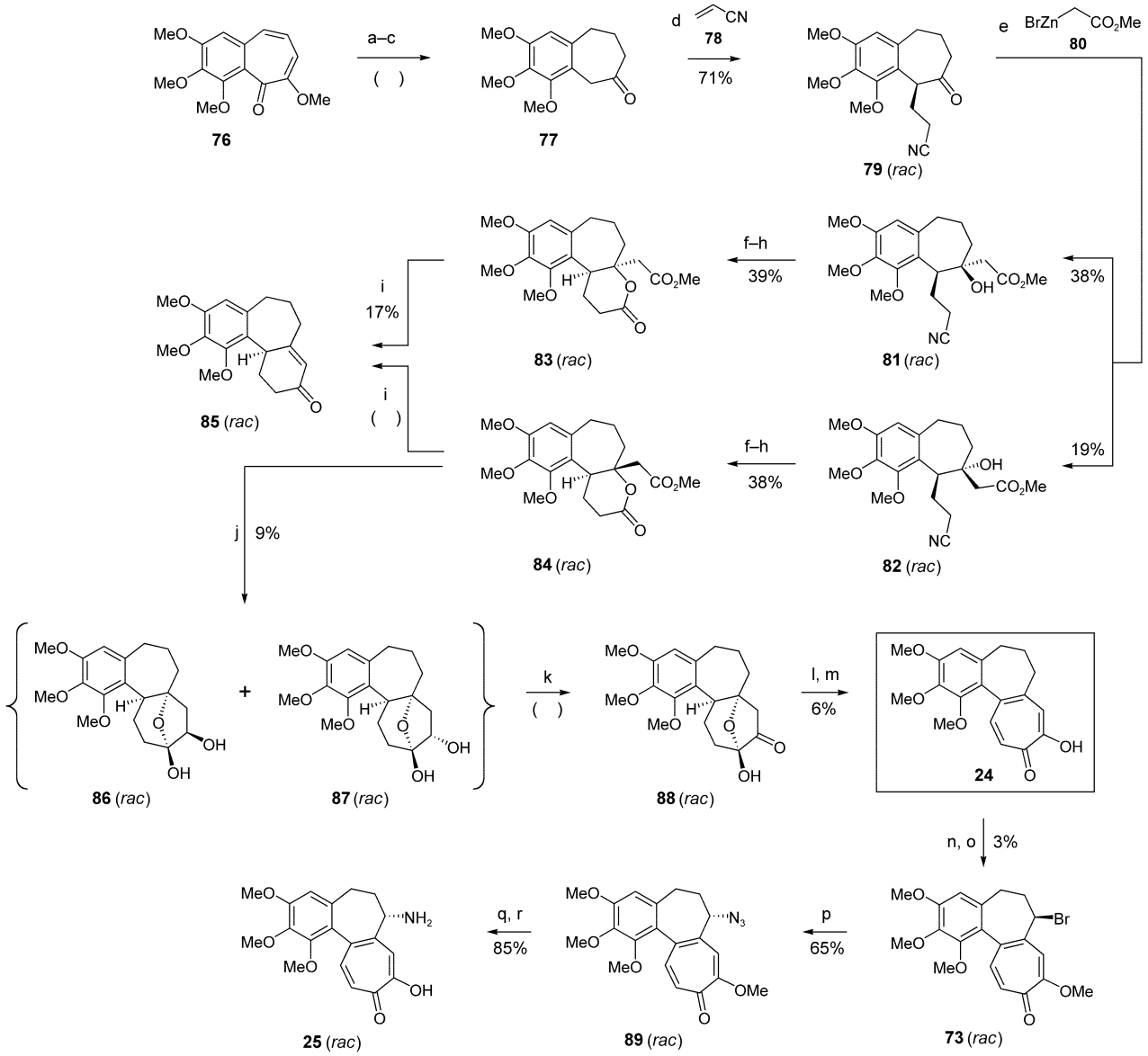
Also in 1959, van Tamelen et al. reported a total synthesis of colchicine which in part followed the same pathway as the strategy Eschenmoser.[26] However, it differs with respect to the central step for the construction of ring C (Scheme 11).

The synthesis started with the preparation of the ketone **77** from tetramethylpurpurogallin (**76**) in analogy to the synthesis discussed above. The alkylation of the reluctant substrate trimethoxybenzosuberone **77** could successfully be realized by using acrylamide (**78**) as a Michael acceptor. In a Reformatsky reaction, the Michael adduct *rac*-**79** was transformed into the diastereomeric products *rac*-**81** and *rac*-**82**, which were separated by chromatography and fractional crystallization. These isomers were separately transformed




***Scheme 10.*** Completion of the synthesis of (±)-colchicine (*rac*-**1**) by Eschenmoser et al. utilizing the relay compound **24**. Reagents and conditions: q) $CH_2N_2$, $Et_2O$, MeOH, 0 °C, 1 h; r) NBS, benzoyl peroxide, $CCl_4$, *hν*, reflux, 18 min; s) $NH_3$, EtOH, $H_2O$, 95–100 °C, 15 h; t) aqueous KOH, EtOH, 130 °C, 23 h; u) $CH_2N_2$, $Et_2O$, $CH_2Cl_2$, MeOH, 0 °C, 30 min; v) $Ac_2O$, pyridine, 100 °C, 15 min. NBS = *N*-bromosuccinimide.




***Scheme 11.*** Synthesis of (±)-trimethylcolchicinic acid (*rac*-**25**) by van Tamelen et al. utilizing the relay compound **24**. Reagents and conditions: a) $LiAlH_4$; b) Zn, $H_2SO_4$; c) $H_2$, Pd/C; d) **78**, KO*t*Bu, MeCN, *t*BuOH, room temperature, 9 h; e) Zn, $I_2$, methyl bromoacetate, benzene, reflux, 3 h; f) KOH, MeOH/$H_2O$, reflux, 21 h; g) DCC, pyridine, room temperature, 2 days; h) $CH_2N_2$, MeOH, $Et_2O$; i) Na, xylene, reflux, 4 h; j) Na, liquid $NH_3$, 20 min; k) $Cu(OAc)_2$, MeOH, reflux, 3 h; l) $TsOH{\cdot}H_2O$, benzene, 5.5 h; m) NBS, $CHCl_3$, reflux, 1 h, 15 min; n) $CH_2N_2$, MeOH; o) NBS, $CCl_4$, *hν*, reflux, 23 min, →RT, 1 h; p) $NaN_3$, MeOH, 90–95 °C, 27 h; q) $H_2$ (1 atm), Pd/C, MeOH, room temperature; r) HCl (aqueous, 1 N), reflux, 2 h.

into the corresponding lactone esters *rac*-**83** and *rac*-**84**. In this case, the lactone acts as an internal protecting group. During the subsequent acyloin condensation, deprotonation of the hydroxy group had to be suppressed to avoid base catalysis of the competing Dieckmann condensation. Under classical conditions for the acyloin condensation, both lactones afforded exclusively the cyclohexenone *rac*-**85** derived from the Dieckmann condensation product. With sodium in liquid ammonia, only the minor lactone isomer *rac*-**84** was converted, to give the condensation products *rac*-**86** and *rac*-**87** in 9% yield.

This mixture of hemiketals was oxidized to give *rac*-**88** and an acid-catalyzed opening of the oxa bridge followed by further oxidation of the resulting dihydrotropolone with NBS afforded desacetamidocolchiceine (**24**). Again, the colchiceine derivative **24** was used as a relay compound and was brominated at C7 by the method of Eschenmoser to give *rac*-**73**. In contrast to the direct ammonolysis, the introduction of the amino function *via* the azide *rac*-**89** proceeded in good yield. Hydrogenation of the azide function and cleavage of the tropolone methyl ether were also carried out in excellent yield to give trimethylcolchicinic acid (*rac*-**25**).

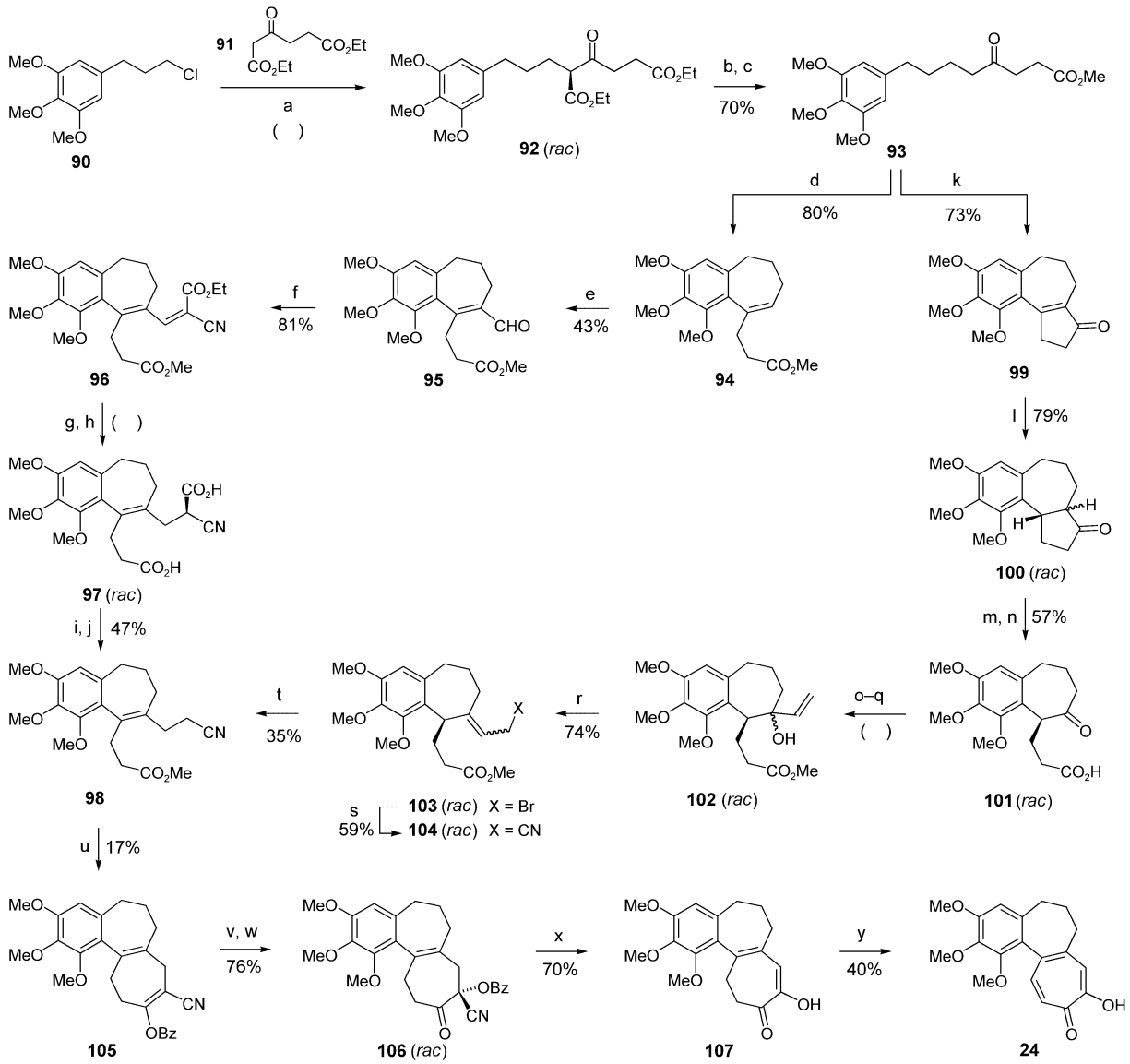
Although the synthesis addressed the problem of selective oxygenation at C9 and C10, the construction of ring C, on the other hand, could only be accomplished in very low yields both in the key reaction (acyloin condensation) and the subsequent oxidation steps.

### *4.4. The Roussel–Uclaf Synthesis*

The Roussel–Uclaf synthesis of desacetamidocolchiceine (**24**) (Scheme 12) reported in 1965 by Toromanoff and co-workers strategically resembles the approach of van Tamelen and co-workers, but brought about improvements with respect to the critical points mentioned above.[31] Ring B was condensed to the aromatic ring A in a Friedel–Crafts-type cyclization (A→AB→ABC).

The synthesis started with the preparation of the ketoester **93** from which either of the Friedel–Crafts products **94** or **99** could be obtained under Brønsted acidic conditions. Both compounds were converted into the cyanoester **98** in satisfying yields, either in a six-step sequence from **94** or in nine steps from **99**. The use of the cyanoester rather than the corresponding diester was of advantage because it guaranteed the formation of the Dieckmann condensation product in a regioselective manner. The product of this key reaction was isolated as the enolbenzoate **105** in only 17% yield. The free enolate anion derived from **105** was oxygenated at the α position and subsequently transformed into the dihydrotropolone **107**, which had already been used as an intermedi-




***Scheme 12.*** Roussel–Uclaf synthesis of desacetamidocolchiceine (**24**). Reagents and conditions: a) **91**, Na, benzene, reflux, 6 h, →RT, 14 h; b) NaOH, MeOH/$H_2O$; then aqueous HCl; c) $CH_2N_2$, $CH_2Cl_2$; d) TsOH, benzene, reflux, 16 h; e) *N*-methylformanilide, $POCl_3$, 55–60°C, 4 h; f) ethyl cyanoacetate, piperidine, HOAc, benzene, reflux, 20 h; g) $H_2$ (1 atm), $PtO_2$, EtOH, room temperature, 1 h; h) KOH, MeOH, room temperature, 17 h; i) 180–200°C; j) $CH_2N_2$, $CH_2Cl_2$; k) 85% $H_3PO_4$, 50°C, 16 h; l) Na, $NH_3$, THF, −70°C, 1 h 35 min; m) NaOEt, EtOH, isoamylnitrite, 0°C, 1 h 20 min; then HOAc; n) pyruvic acid, HOAc/$H_2O$, <100°C, 2 h; o) $C_2H_2$, Na, liquid $NH_3$, −70°C, 2.5 h; then addition of *rac*-**101**, THF, −40°C, 5.5 h; p) $H_2$ 1 atm, Pd/$CaCO_3$, pyridine, DMF, room temperature; q) $CH_2N_2$; r) $PBr_3$, $CHCl_3$/ligroin, −20→−10°C, 5 h; s) CuCN, DMSO, 50°C, 25 h; t) 2,4-dinitrobenzenesulfonic acid, benzene, reflux, 2 h; u) K, toluene, reflux, 2 h; then BzCl, pyridine, 10°C, →RT, 2 h; v) KOH, MeOH/$H_2O$, room temperature, 16 h; w) Na, benzene, reflux, 15 h; then benzoyl peroxide, room temperature, 14 h; x) aqueous $NaHCO_3$, EtOH/$H_2O$, reflux, 10 min; y) NBS, reference [26]. DMF = *N*,*N*-dimethylformamide; DMSO = dimethyl sulfoxide; Bz = Benzoyl.

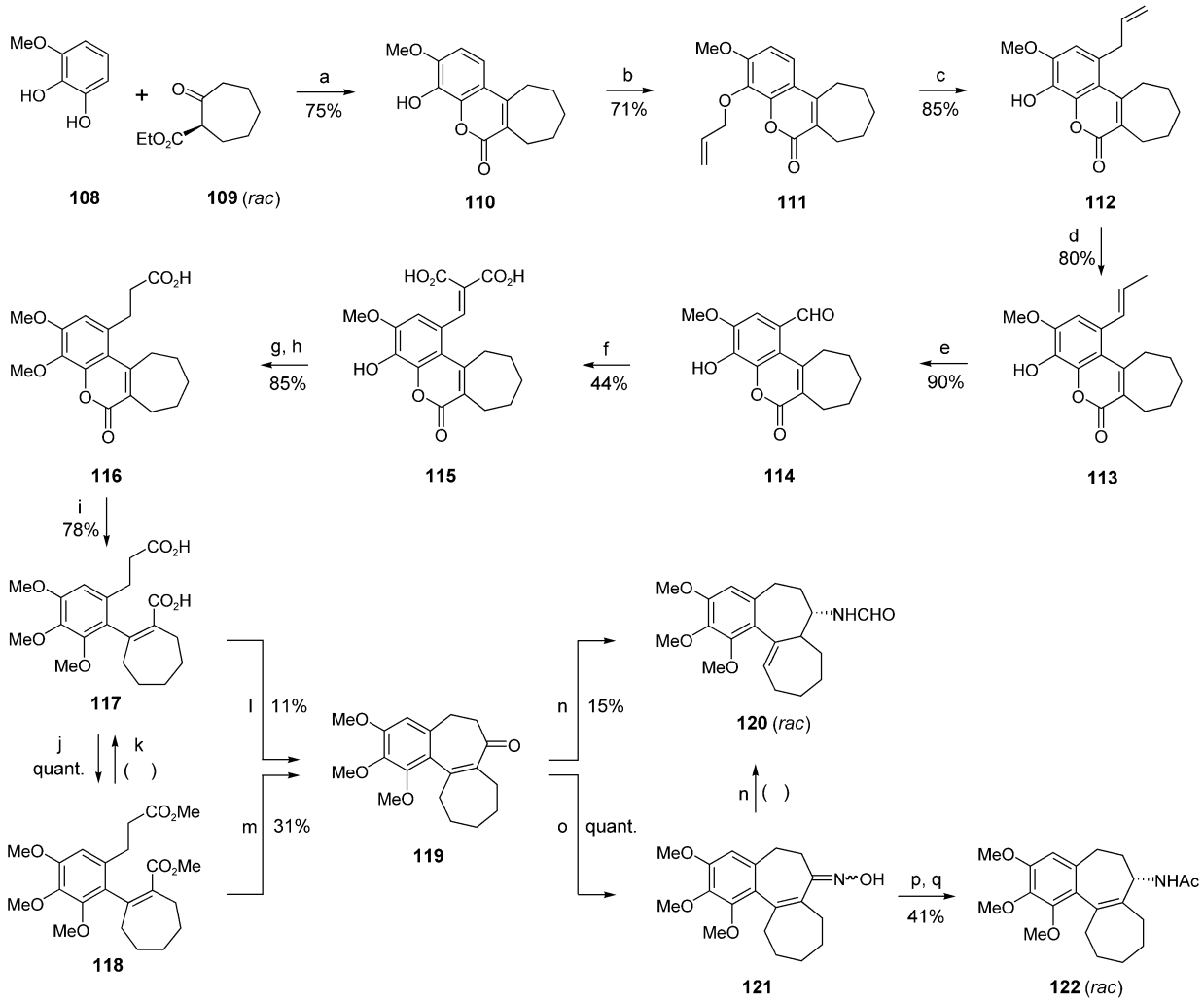
ate by van Tamelen et al. The oxidation of **107** to desacetamidocolchiceine (**24**) with NBS completed the formal total synthesis of **1**.

All in all, the selective construction of the C9, C10 oxygenated tropolone was improved. Nevertheless, selective functionalization at C-7 had still not been implemented.

### 4.5. The Sankyo Synthesis

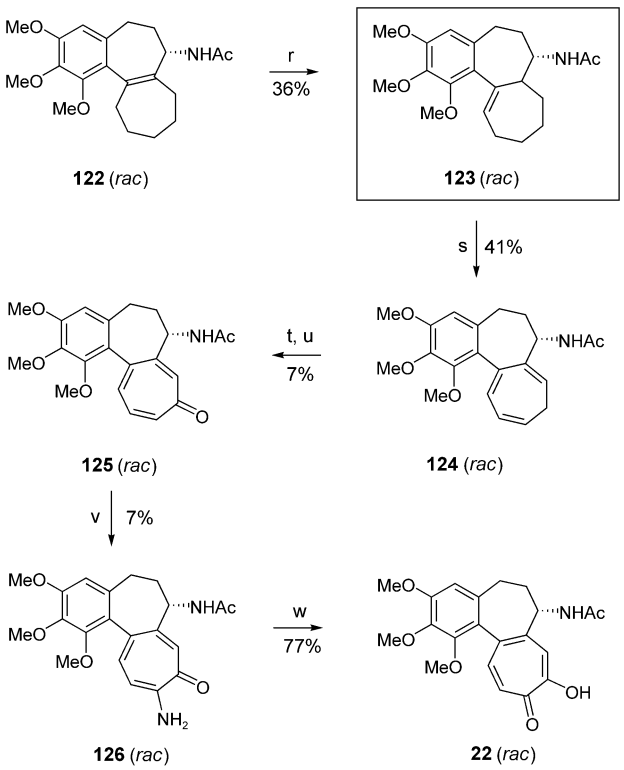
The problem of the selective functionalization at C7 was addressed in the Sankyo synthesis of colchiceine (**22**) reported by Nakamura et al. in 1962 (Schemes 13 and 14).[28] In this synthesis, the amino group was introduced prior to the oxidation of ring C to a tropolone. The strategy was actually based on previous works of Boekelheide et al.[24c] and focused on the functionalization of C7 by formation of the strategic C6–C7 bond in ring B (AC→ABC).

As shown in Scheme 13, pyrogallol mono(methyl ether) **108** was first treated with the suberone *rac*-**109** in a Pechmann condensation to give the coumarin **110**. The seven-membered ring later serves as a precursor for ring C. The coumarin also contains a carbonyl function, which is later required for the cyclization of ring B. The free phenol functionality was transformed into an allyl ether (**111**) and subsequent Claisen rearrangement (→**112**) allowed the selective introduction of a side chain for the projected construction of ring B. The propanoic acid side chain was established in five subsequent steps. Hydrolysis of the coumarin **116** afforded the dicarboxylic acid **117.** Methylation provided the diester **118**, which proved to be a better starting material than **117** for the crucial cyclization step (decarboxylative Dieckmann condensation). The product of this cyclization (**119**) already contains the complete 6,7,7-membered carbocyclic scaffold. To introduce the nitrogen function at C7, a Leuckart–Wallach reaction was used to give the formamide *rac*-**120** with a concomitant shift




***Scheme 13.*** Sankyo synthesis of the colchicine intermediate *rac*-**122**. Reagents and conditions: a) $MeSO_3H$, room temperature, 20 h; b) allyl bromide, $K_2CO_3$, NaI, $MeOH/H_2O$, reflux, 16 h; c) *N*,*N*-dimethylaniline, reflux, 6 h; d) KOH, MeOH, 110–120 °C, 6 h; e) $O_3$, $CH_2Cl_2$, −60 °C, 1 h; f) malonic acid, pyridine, aniline, 50 °C, 22 h; g) $H_2$, Pd/C, MeOH, 1 h; h) 180 °C, 1 mm Hg, 8 h; i) $Me_2SO_4$, KOH, <100 °C, 3 h, →RT, 14 h; j) $CH_2N_2$, $MeOH/Et_2O$, room temperature, 1 h; k) KOH, $MeOH/H_2O$, reflux, 2 h; l) KOAc, $Ac_2O$, reflux, 2 h, →138 °C, 20 h; m) KO*t*Bu, *t*BuOH, xylene, 139 °C, 20 h; n) $HCO_2H$, $CO(NH_2)_2$, 110→180 °C over 6 h; o) $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux, 20 h; p) $LiAlH_4$, THF, reflux, 6 h; q) $Ac_2O$, pyridine, room temperature, 12 h.

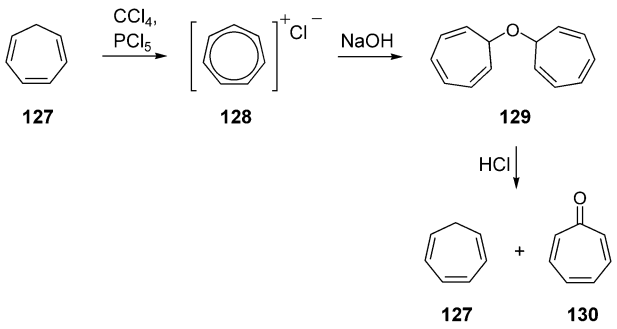



***Scheme 14.*** Completion of the Sankyo synthesis of (±)-colchiceine (*rac*-**22**). Reagents and conditions: r) $BF_3{\cdot}OEt_2$, benzene, room temperature, 60 h; s) NBS, $CCl_4$, reflux, 5 min; then collidine 160–180 °C, 2 h; t) $PCl_5$, $CCl_4$, room temperature, 24 h; u) aqueous NaOH, 0 °C; then conc. HCl, room temperature, 3 days; v) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 7.5 h; w) aqueous NaOH

of the C–C double bond. Alternatively, the corresponding oxime **121** was reduced and the resulting amine subsequently converted into the acetamide *rac*-**122**.

The synthesis was completed by using either synthetic *rac*-**123**, which was available by $BF_3{\cdot}OEt_2$-mediated double-bond isomerization of *rac*-**122** (Scheme 14), or enantiomerically pure material obtained from natural colchicine as a relay compound. The cycloheptene *rac*-**123** was converted into the tropilidene *rac*-**124** in a bromination/dehydrobromination sequence. As the direct oxidation of *rac*-**124** to the tropone *rac*-**125** was not viable with the various methods tried, a fairly wasteful deviation had to be made. The Nozoe method for tropone synthesis via a ditropyl ether that was applied is illustrated in Scheme 15.[49] First, an intermediate tropylium salt **128** was generated by hydride abstraction from cycloheptatriene (**127**). Reaction with NaOH then gave a ditropyl ether **129**, which upon treatment with concentrated HCl disproportionated to afford a mixture of the starting tropilidene (**127**) and the oxidation product, tropone (**130**).

The corresponding reaction of *rac*-**124** afforded the desired tropone *rac*-**125**, albeit in a disappointing low yield (Scheme 14). One can suspect that not only the desired colchicide *rac*-**125** but also regioisomeric products were formed in this step. Without further purification, crude *rac*-**125** was treated with hydrazine, presumably again with the formation of a mixture of regioisomers, from which colchi-




***Scheme 15.*** Tropone synthesis via a ditropyl ether.

ceineamide *rac*-**126** could be isolated in pure form (again in very low yield). Saponification of the aminotropone finally furnished (±)-colchiceine (*rac*-**22**).

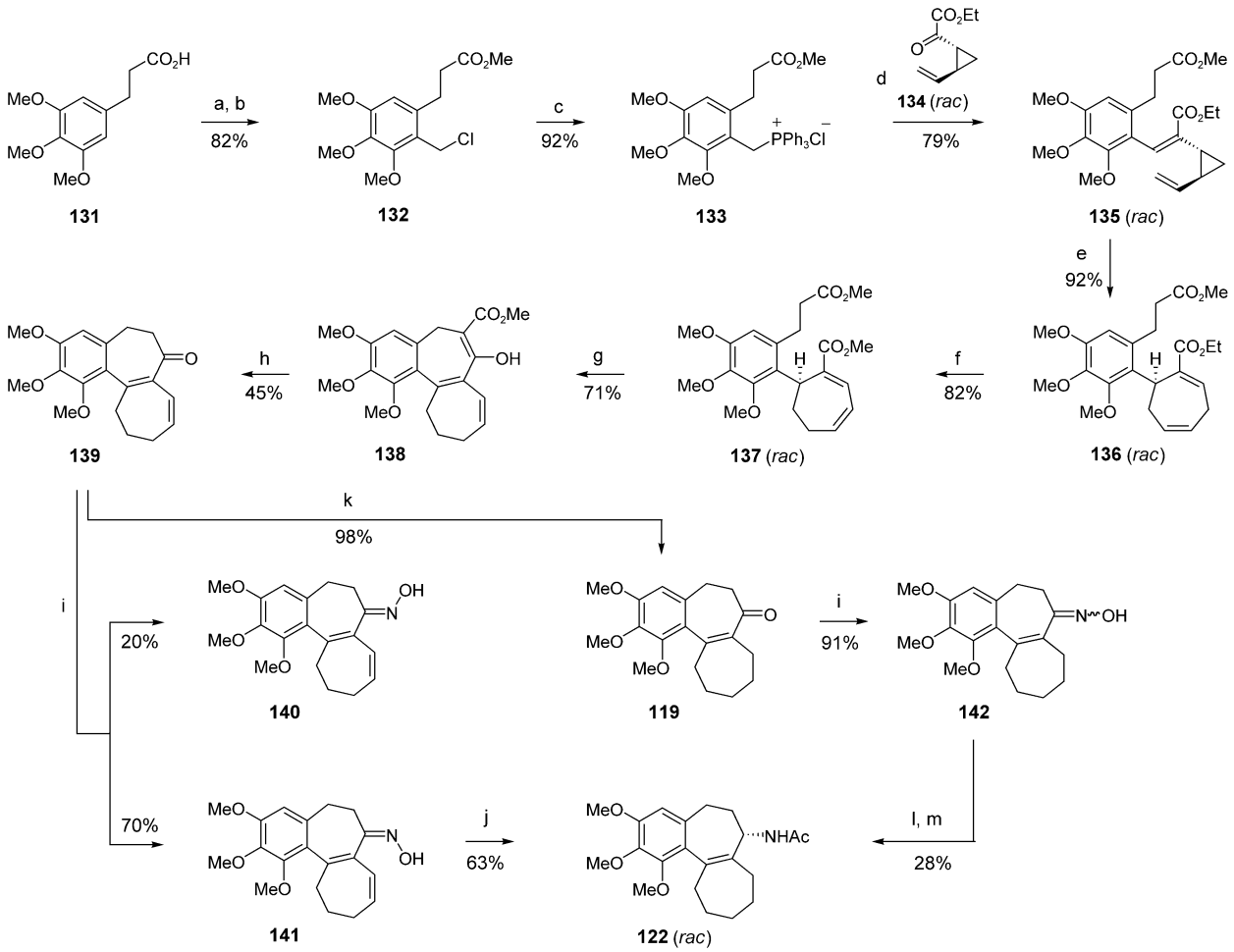
#### *4.5.1.* ***Synthesis of an Advanced Colchicine Intermediate by Wenkert et al.***

Wenkert et al. reported an alternative synthesis of the key intermediates **119** and *rac*-**122**, which had already occurred in the Sankyo synthesis.[37] The Wenkert approach differs from the Sankyo synthesis mainly in the way that the Dieckmann condensation precursor, that is, the diester *rac*-**137**, is prepared (Scheme 16). For the construction of the seven-membered ring C, a divinylcyclopropane rearrangement was applied.

The hydrocinnamic acid **131** was used as starting material. The precursor *rac*-**135** required for the cyclization of ring C was prepared by a Wittig reaction from *rac*-**134** and the phosphorane obtained from **133**. The subsequent [3,3] sigmatropic rearrangement proceeded in high yield, and the diester *rac*-**137** was obtained after a shift of the remote C–C double bond in *rac*-**136** and subsequent esterification. Further conversion into the ketone **139** by Dieckmann condensation and demethoxycarbonylation was achieved in a yield comparable to that of the analogous transformation described by Nakamura (32 %). The diastereomeric oximes **140** and **141** obtained from the ketone **139** could be separated, and the major *Z* isomer **141** was transformed into the acetamide *rac*-**122** by catalytic hydrogenation with concomitant *N*-acetylation. As a second point of overlap with the Sankyo synthesis, the key intermediate **119** was reached by catalytic hydrogenation of **139**. Reduction of the corresponding oxime mixture (**142**) with lithium aluminum hydride followed by acetylation also provided *rac*-**122**. At this stage the synthetic study was concluded, constituting a formal total synthesis of racemic colchicine.

Both the synthesis of Wenkert (Scheme 16) and the Sankyo synthesis (Schemes 13 and 14) provided an improved solution for the problem of C7 functionalization. While focusing on this problem, regioselectivity in the construction of the tropolone ring C was strategically neglected, and the overall efficiency of the synthetic schemes was spoiled by substantial losses of material during the completely unselective introduction of functionality in ring C following the strategy of Nakamura et al.




***Scheme 16.*** Synthesis of colchicine intermediates **119** and *rac*-**122** by Wenkert et al. Reagents and conditions: a) $Me_2SO_4$, $K_2CO_3$, acetone, reflux, 2 h; b) $MeOCH_2Cl$, $CHCl_3$/HOAc, 20 °C 18 h; c) $PPh_3$, benzene, reflux, 24 h; d) LDA, THF, −10 °C, →20 °C, 3 h, then *rac*-**134**, THF, −10 °C, →RT, 3 h; e) xylene, reflux, 24 h; f) NaOMe, MeOH, reflux, 12 h; then $CH_2N_2$, $Et_2O$; g) NaOMe, xylene, reflux, 12 h; h) 5% HCl, HOAc, $H_2O$, dioxane, reflux, 4 h; i) $NH_2OH$·HCl, pyridine, EtOH, reflux, 2 h; j) $H_2$, Pd/C, $Ac_2O$; k) $H_2$ (3 atm), Pd/C, EtOAc, room temperature, 2 h; l) $LiAlH_4$, THF, reflux, 12 h; m) $Ac_2O$, pyridine, room temperature, 16 h. LDA = lithium diisopropylamide.

### *4.6. Synthesis of Desacetamidocolchiceine through [4+3] Cycloaddition by Boger and Brotherton*

In contrast to the approaches discussed above, Boger and Brotherton developed a very direct entry to annulated tropone structures by means of a cycloaddition strategy ABC′→ABC (Scheme 17).[36]

The cycloaddition of the Eschenmoser α-pyrone **54** and the cyclopropenone ketal **143** gave either the Diels–Alder product *rac*-**144** (which could not be converted into the desired tropone) or the [4+3] cycloaddition product *rac*-**146**, depending on the reaction conditions chosen. Upon heating, the cyclopropenone ketal **143** is in thermal equilibrium with a reactive open chain species, which according to Boger is best described as a nucleophilic delocalized vinyl carbene (**150**/**151**; Scheme 18).

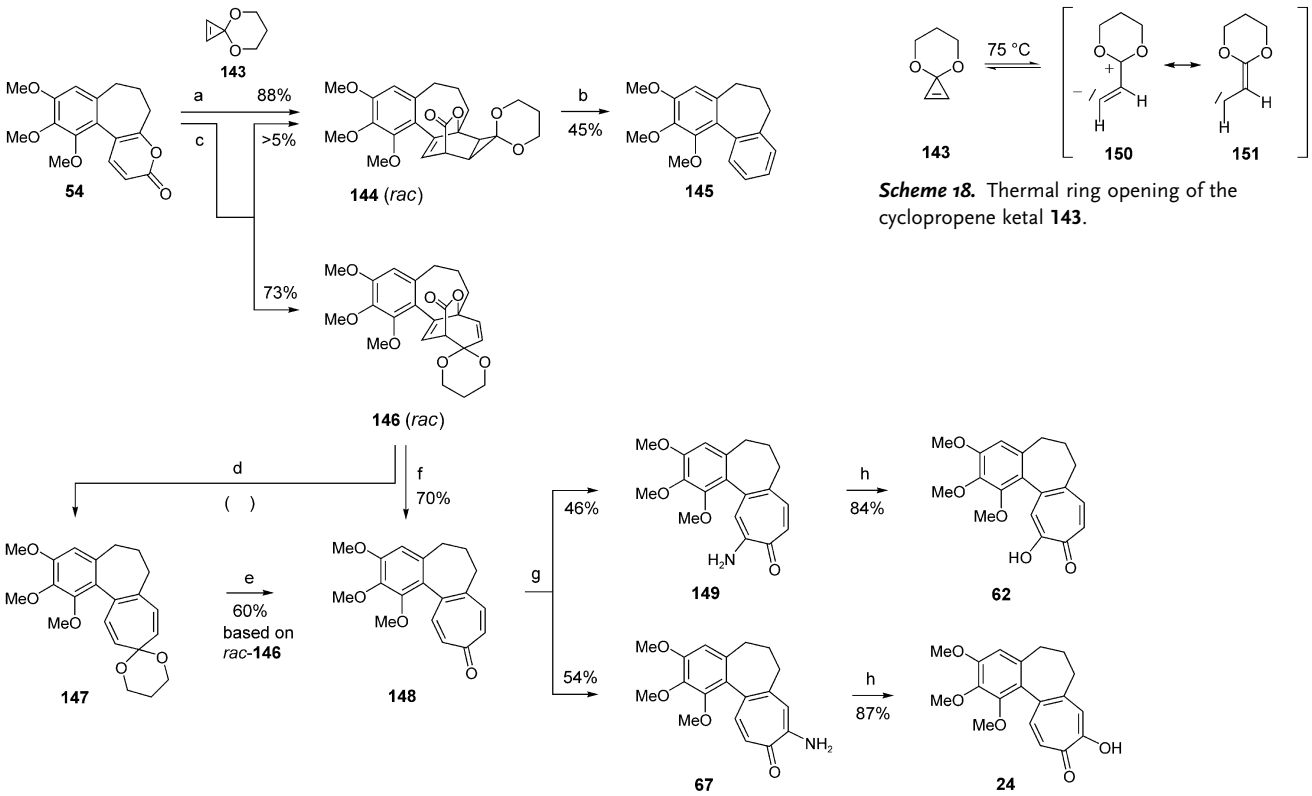
The [4+3] cycloaddition product **146** could easily be transformed into the tropone **148** in good yield through a retro-Diels–Alder decarboxylation and subsequent hydrolysis of the ketal function (Scheme 17). A one-pot procedure was used to increase the yield to 70% (*rac*-**146**→**148**). α Functionalization of **148** with hydrazine according to Nozoe et al. afforded the regioisomeric aminotropones **149** and **67**, which could be separately converted into the regioisomeric tropolones **62** and **24** (desacetamidocolchiceine), respectively, by saponification.

The sequence elaborated by Boger (**54**→**24**) greatly abbreviates the Eschenmoser synthesis. Although the route was very efficient, the unselective α oxygenation of the tropone intermediate **148** still remained a strategic drawback.

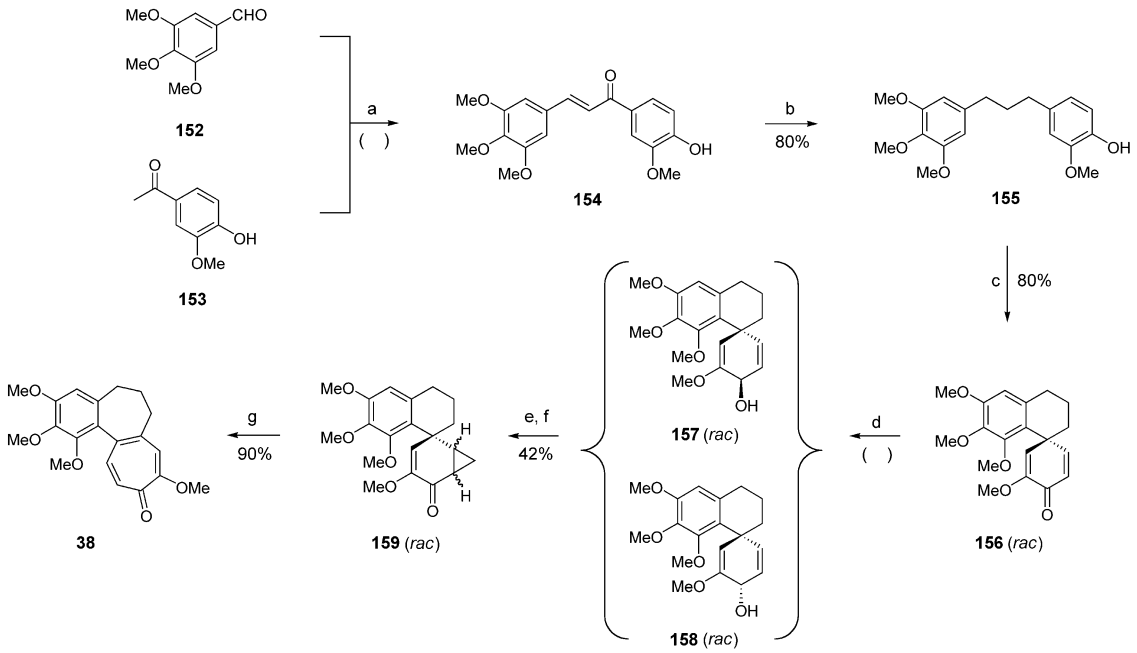
### *4.7. Synthesis of Desacetamidoisocolchicine by Skeletal Rearrangement According to Tobinaga and Co-workers*

A rather striking strategy, completely different to all previous approaches, was described by Tobinaga and co-workers (Scheme 19).[34] Their synthesis of desacetamidoiso-




***Scheme 17.*** Synthesis of desacetamidocolchiceine (**24**) by Boger and Brotherton. Reagents and conditions: a) **143**, 6.2 kbar, 25 °C, 5 days, b) mesitylene, 200 °C, 50 min; c) **143**, benzene, 75 °C, 36 h; d) 200 °C, 2 min; e) HOAc, $H_2O$, THF, 25 °C, 5 min; f) HOAc, $H_2O$, THF, 100 °C, 3.5 h; g) $N_2H_4 \cdot H_2O$, EtOH, 0 → 25 °C, 4.5 h; h) KOH (aqueous, 2 N), EtOH, 100–110 °C, 21 h.




***Scheme 19.*** Synthesis of desacetamidoisocolchicine (**38**) by Tobinaga and co-workers Reagents and conditions: a) condensation, no conditions given; b) catalytic hydrogenation, no conditions given; c) anodic oxidation, $HBF_4$, MeCN, 20 min; d) $NaBH_4$; e) $CH_2I_2$, Zn/Cu couple; f) Jones oxidation; g) $Ac_2O$, $H_2SO_4$, room temperature.

colchicine (**38**) along the lines of a rearrangement strategy AC′→AB′C′→ABC is based, like the Scott synthesis, on a false hypothesis concerning the biosynthesis of colchicine.[50]

The synthesis started from the simple aromatic compounds **152** and **153**. The chalcone **154** prepared from these simple building blocks was hydrogenated and the intermediate **155** was cyclized in an electrochemical oxidation to the spirocyclic dienone *rac*-**156**. Reduction with sodium borohydride afforded a mixture of the diastereomeric alcohols *rac*-**157** and *rac*-**158**, which was transformed into the cyclopropane derivative *rac*-**159** by Simmons–Smith cyclopropanation and subsequent Jones oxidation. Although the stereostructure of *rac*-**159** remained unknown, treatment with an $Ac_2O/H_2SO_4$ mixture directly gave rise to **38**. Evidently, the opening of the cyclopropane ring in *rac*-**159** was accompanied by a migration of the aryl residue followed by dehydration to give the tropolone methyl ether **38** (migration of the alkyl residue would have resulted in the formation of a regioisomeric tropolone).

This single operation served to unfold the complete 6,7,7-membered ring skeleton establishing the tropolone ring C with the desired oxidation state. Furthermore, the desired regioisomer of the tropolone methyl ether required for the C7 functionalization according to Eschenmoser was generated selectively. Nevertheless, both the synthesis of Boger and Brotherton and the synthesis of Tobinaga and co-workers are inefficient, as they rely on this low-yielding and non-stereoselective introduction of the amido functionality.

#### 4.8. The Evans Synthesis of (±)-Trimethylcolchicinic Acid

Inspired by the interesting work of Tobinaga and co-workers, Evans et al. reported a synthesis of the Eschenmoser intermediate **38** in 1978 in which they further investigated the rearrangement transformation.[35a] Three years later, the Evans group came up with a very convincing total synthesis of trimethylcolchicinic acid following a AC′→ABC strategy in which the problems of the construction of the tropolone ring and the introduction of C7 functionality were equally well-addressed (Scheme 20).[35b]

The main innovation was that the precursor *rac*-**167** for the key transformation, that is, the skeletal rearrangement, only contains rings A and C′. Intermediate *rac*-**167** was prepared in a convergent fashion and in high yield from the cyclohexenone derivative *rac*-**163** and the arylbutanoate **165**. The synthesis of *rac*-**163** started with the electrochemical oxidation of trimethoxybenzene **160** to give **161**, which was selectively hydrolyzed to the quinone monoketal **162**. Subsequent methylenation with dimethylsulphoxonium methylide afforded *rac*-**163**. The arylbutanoate **165** in turn was obtained by chain elongation of the trimethoxycinnamate **44**. Coupling of the ester enolate derived from **165** with the building block *rac*-**163** afforded a mixture of diastereomers (*rac*-**166**), which was directly hydrolyzed to give the cyclization precursor *rac*-**167**.

The subsequent key transformation was performed with very high yield in a one-pot procedure or, alternatively, via *rac*-**168** under milder conditions. The rearrangement proceeded in analogy to the transformation designed by Tobinaga et al., with the difference that the presence of the additional ester function resulted in the formation of **169** as well as the expected product *rac*-**170**. The mixture of these isomeric products was treated with DDQ to give a 3:7 mixture of the heptafulvene **171** and the desired tropolone methyl ether *rac*-**172**. These two oxidation products were separated, and it was found that they can be readily equilibrated back to the initial 3:7 mixture. Hydrolysis of the ester and decarboxylation of *rac*-**172** gave rise to the Eschenmoser intermediate **38**. For the conclusion of the formal total synthesis, the isomeric mixture **171**/*rac*-**172** was converted in a three-step sequence into the advanced colchicine precursor *rac*-**25** by hydrolysis of the ester, Curtius degradation, and demethylation.

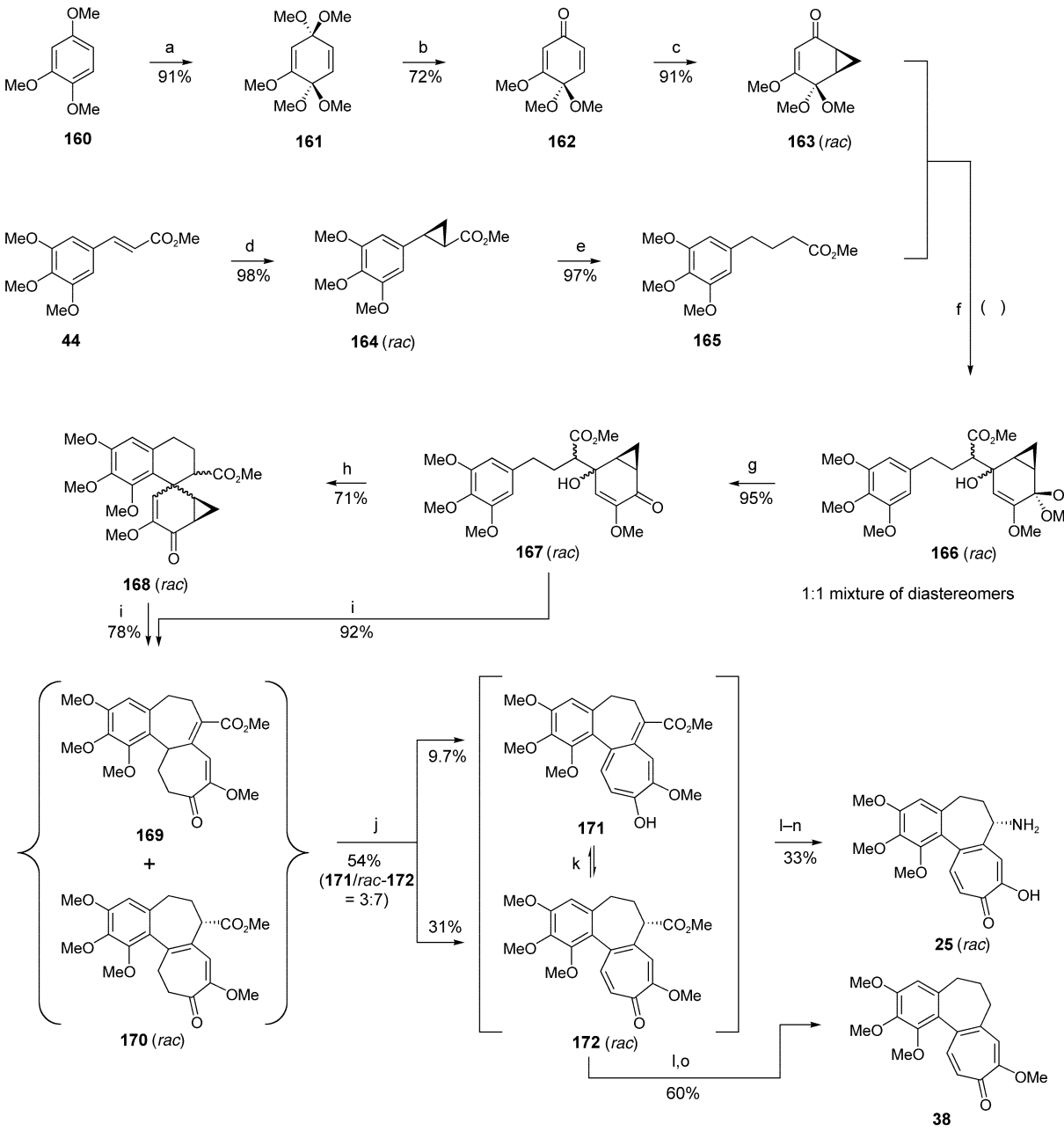
In conclusion, the synthesis of Evans et al. provided an outstanding solution for the construction of the unusual 6,7,7-membered ring system and included the selective functionalization of both rings C and B. The unsatisfactory yield for the generation of the tropolone remained a shortcoming in this synthesis. Also, the development of an enantioselective variant seemed extremely difficult owing to the facile equilibration of **172** and its isomer **171**.

#### 4.9. The Woodward Synthesis

One of the most innovative studies in the field of colchicine synthesis was presented by Woodward in 1963 as a Harvey Lecture.[29] A remarkable feature of his synthesis was the implementation of the nitrogen functionality at C7 as an integral part of the synthetic strategy. The crucial role in the very straightforward synthetic concept was played by the isothiazole ring, a heterocycle first described in the course of this synthesis. It served as a masked amino function and acted as platform for the cyclization of rings B and C (Scheme 21).

The disubstituted isothiazole **174** was obtained by treatment of the β-aminocrotonate **173** with thiophosgene. Photobromination and reaction with triphenylphosphane afforded the phosphonium salt **175**, which was used for the Wittig olefination of trimethoxybenzaldehyde **152**. After reduction of the C–C double bond with diimine (the isothiazole sulphur atom precluded the use of catalytic hydrogenation) and conversion of the ester into an aldehyde, the resulting intermediate **177** was subjected to a second Wittig reaction with the phosphorane **178**. Saponification and isomerization of the *Z*/*E* mixture of isomers afforded the *E*,*E*-dienecarboxylic acid **179** as a pure stereoisomer. Cyclization to form ring B was achieved in a Friedel–Crafts-type alkylation, and subsequent reduction with diimine afforded *rac*-**181**. In the following step, the heterocycle was lithiated at the unsubstituted position and carboxylated with $CO_2$. The corresponding diester *rac*-**182** then served as a precursor for the cyclization of ring C in a Dieckmann condensation. Subsequent decarboxylation gave the tetracyclic ketone *rac*-**183**. C10 was functionalized by Woodward's method for the introduction of a 1,3-dithiane. For this purpose, the position

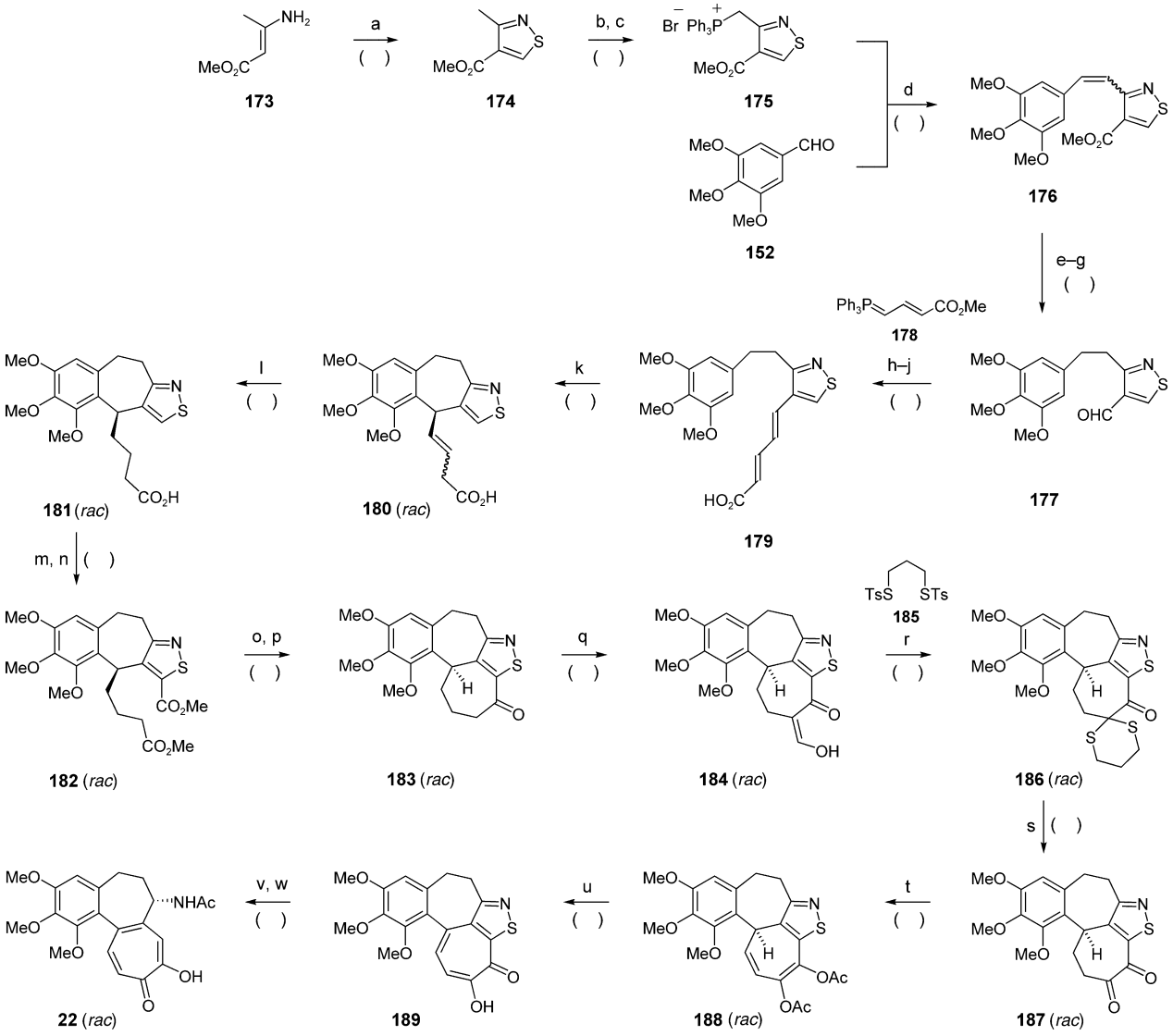



***Scheme 20.*** Synthesis of (±)-trimethylcolchicinic acid (*rac*-**25**) by Evans et al. Reagents and conditions: a) KOH, MeOH, anodic oxidation, 0 °C, 25 h; b) $(CO_2H)_2$, THF/$H_2O$, room temperature, 12 min; c) $Me_3S(O)I$, NaH, DMSO, 0 °C, 15 min, →RT, 30 min, then **162**, DMSO, room temperature, 2 h; d) $CH_2N_2$, $Pd(OAc)_2$, $Et_2O/CH_2Cl_2$, 0 °C, 15 min; e) $H_2$ (51 psi), Pd/C, MeOH; f) **165**, LDA, THF, −78 °C, 35 min, then *rac*-**163**, →0 °C, 30 min; g) aqueous $(CO_2H)_2$, THF, room temperature, 5 h; h) $CF_3CO_2H$, room temperature, 20 min; i) $CF_3CO_2H$, reflux, 35 min; j) DDQ, benzene, reflux, 18 h; k) $CDCl_3$, room temperature, 24 h, equilibration to a 3:7 mixture of **171**/*rac*-**172**; l) NaH, MeOH/$H_2O$, 75 °C, 45 min; m) $(PhO)_2P(O)N_3$, $NEt_3$, *t*BuOH, reflux, 17 h; n) HCl (aqueous, 3 N), 110 °C, 90 min; o) 180 °C, 1–2 min. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

α to the carbonyl group of *rac*-**183** was first activated by formylation (→*rac*-**184**) before reaction with the bisthiotosylate **185** gave rise to the dithiane *rac*-**186**. Hydrolysis of *rac*-**186** afforded the α-diketone *rac*-**187**, which was converted into the dienol diacetate *rac*-**188**. Remarkably, a spontaneous aerial oxidation under basic conditions yielded the desired tropolone **189**. To liberate the amino function, desulphurization was performed with Raney nickel, and (±)-colchiceine (*rac*-**22**) was obtained after acetylation.

Although this synthesis is 40 years old, it demonstrates how selectivity problems can be overcome in a masterly fashion with conceptual creativity. Unfortunately, Woodward did not report yields in his publication, so that the overall efficiency and any possible obstacles cannot be judged.



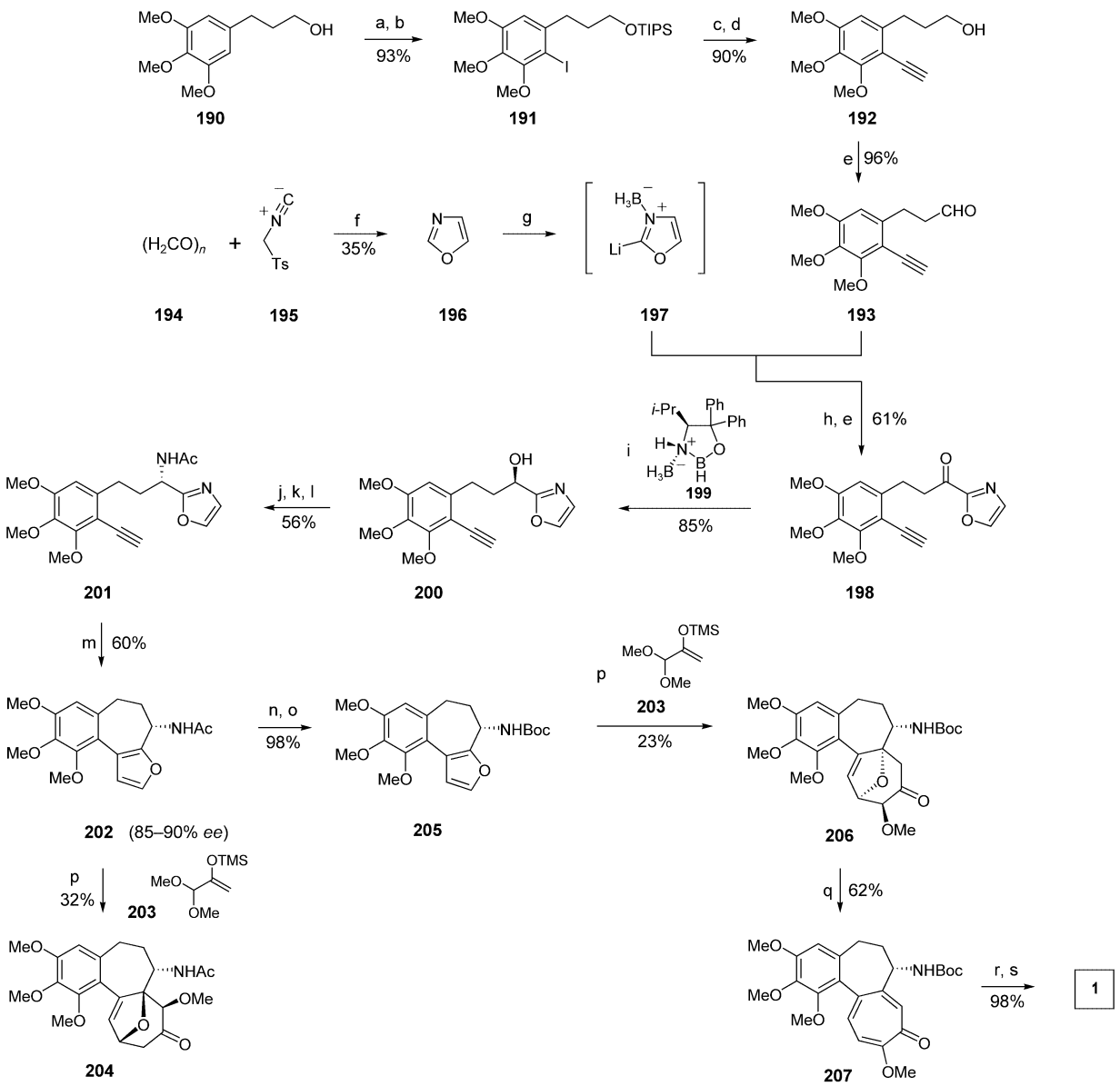
***Scheme 21.*** Synthesis of (±)-colchiceine (*rac*-**22**) by Woodward et al. Reagents and conditions: a) $CSCl_2$, $NEt_3$, $Et_2O$; b) NBS, $CCl_4$, $h\nu$; c) $PPh_3$; d) NaOMe; then **152**; e) $N_2H_4$, $H_2O_2$, $Cu^{II}$; f) $LiAlH_4$; g) $MnO_2$; h) Wittig olefination; i) NaOH aq.; j) $I_2$, $h\nu$; k) 70% $HClO_4$, 60°C; l) $N_2H_4$, $H_2O_2$, $Cu^{II}$; m) *o*-lithiobiphenyl, THF; then $CO_2$; n) esterification; o) NaH, dioxane; p) HOAc, $H_2SO_4$, heating; q) NaH, $HCO_2Et$, EtOH, THF; r) **185**, KOAc, *i*PrOH, reflux; s) $Hg(OAc)_2$, aqueous $HClO_4$, HOAc, heating; t) $Ac_2O$, pyridine; u) NaOH, air; v) Raney Ni, aqueous NaOH; w) $Ac_2O$, pyridine; then aqueous NaOH.

### *4.10. The Cha Synthesis of (−)-Colchicine by Oxyallyl [4+3] Cycloaddition*

In a much more recent synthesis, Cha et al. also made intensive use of heterocyclic chemistry. The annulated furan **202** was used as the central intermediate for a cycloaddition, corresponding to the general ABC′→ABC strategy (Scheme 22).[39]

The starting material, alcohol **190**, was first protected, then iodinated, coupled with TMS-acetylene in a Sonogashira coupling, and finally desilylated (deprotected) to give **192**. A subsequent Swern oxidation afforded the aldehyde **193** in high overall yield. Oxazole (**196**), which was prepared by condensation of TosMIC (**195**) with formaldehyde, served as the second building block. Compound **196** was first converted into the borane adduct to assure regioselective lithiation and to avoid cleavage of the heterocycle. The product obtained from the reaction of the intermediate **197** with the aldehyde **193** was directly oxidized under Swern conditions, and the resulting ketone **198** was enantioselectively reduced to the alcohol **200** with the (*S*)-diphenylvalinol-derived oxazaborolidine **199** following the Itsuno protocol. The transformation to **201** was carried out through Mitsunobu reaction with DPPA as an azide source, Staudinger reduction to the amine, and *N*-acetylation. Upon heating of **201**, the furan **202** was formed in an intramolecular Diels–Alder/retro-Diels–Alder reaction cascade under extrusion of HCN. Whereas the following key step, the cycloaddition of **202** with an oxyallyl



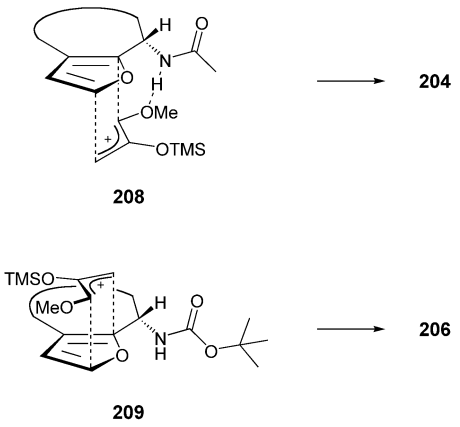
***Scheme 22.*** Synthesis of (−)-colchicine (**1**) by Cha and co-workers. Reagents and conditions: a) TIPSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, →RT, 5 h; b) $I_2$, $Ag(CF_3CO_2)$, $NaHCO_3$, $CHCl_3$, 3 h; c) HC≡CTMS, $[Pd(PPh_3)_2Cl_2]$, CuI, $Et_2NH$, DMSO, 90 °C, 20 h; d) TBAF, THF, 0 °C, →RT, 7 h; e) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 1 h 15 min; then $NEt_3$, −78→0 °C; f) $(CH_2O)_n$, **195**, $K_2CO_3$, DMSO, room temperature, 5 h; then KOH, ethylene glycol, room temperature, 5 h; g) $BH_3$·THF, THF, room temperature, 1 h; then *t*BuLi, −78 °C, 40 min; h) THF, −78 °C, 3 h; i) $BH_3$·THF, (*S*)-(−)-diphenylvalinol, THF, −78 °C, 20 min, →RT; then **198**, THF, 6 h; j) $(PhO)_2P(O)N_3$, $PPh_3$, DIAD, THF, room temperature, 12 h; k) $PPh_3$, $H_2O$, THF, room temperature, 50 h; l) $Ac_2O$, $NEt_3$, DMAP, $Et_2O$, room temperature, 7 h; m) *o*-dichlorobenzene, reflux, 66 h; n) $Boc_2O$, $NEt_3$, DMAP, $CH_2Cl_2$, 35 °C, 10 h; o) LiOH, THF, 12 h; p) **203**, TMSOTf, $EtNO_2$, −78 °C, 1 h, →−60 °C, 12 h; q) TMSOTf, $NEt_3$, $CH_2Cl_2$, 0 °C, 2 h; r) HCl (1 N), $Et_2O$, room temperature, 1 h; s) $Ac_2O$, $NEt_3$, DMAP, $Et_2O$, 25 °C, 10 h. TIPS = triisopropylsilyl; Tf = trifluoromethanesulfonyl; TMS = trimethylsilyl; TBAF = tetra-*n*-butylammonium fluoride; Boc = *tert*-butoxycarbonyl; DIAD = diisopropylazodicarboxylate; DMAP = 4-dimethylaminopyridine.

generated from **203**, afforded the undesired regioisomer **204**, the analogous [4+3] cycloaddition of the Boc-protected compound **205** proceeded with the reversed regioselectivity. However, the desired product **206** was obtained in a mere 23% yield.

As an explanation for the observed selectivity, the authors assumed a participation of a hydrogen bond in the case of **202** as a substrate (structure **208** in Scheme 23). By changing the *N*-protecting group to Boc (**202**→**205**), such a hydrogen bond does not seem to play a role and steric interactions dominate the selectivity (structure **209**).

The use of related oxa-bridged [4+3]-cycloadducts was introduced by Föhlisch et al. as a generally applicable method for tropone synthesis.[51] The oxygen bridge of **206** was removed by treatment with TMSOTf/$NEt_3$ to furnish the tropolone **207** with the correctly placed methyl ether func-




***Scheme 23.*** Influence of the amide function on the regio- and stereoselectivity of the cycloadditions to give **204** and **206**.

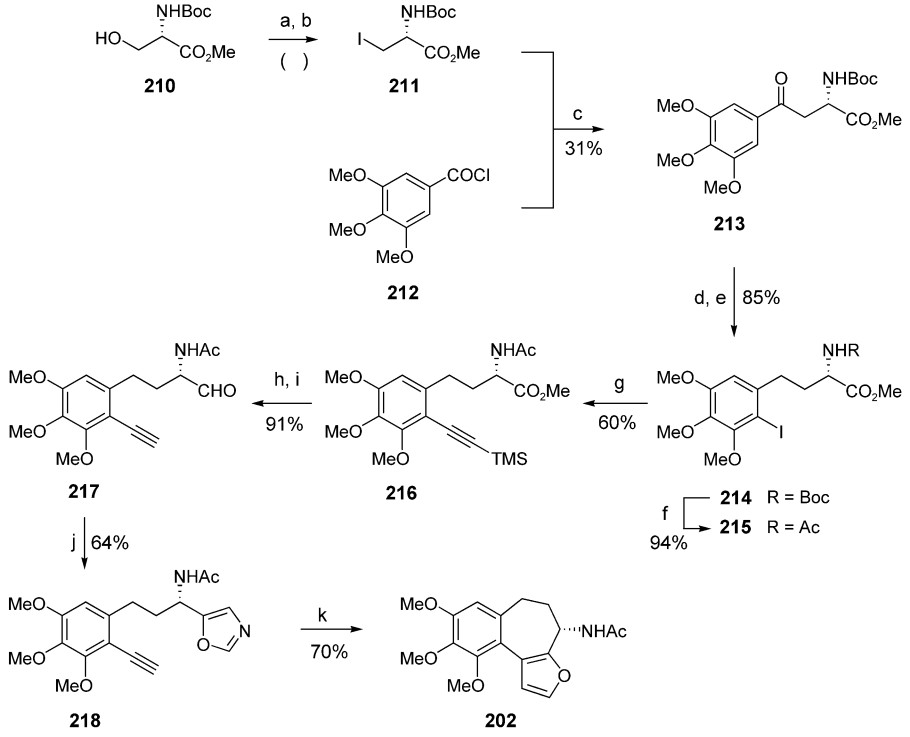
tionality (Scheme 22). After *N*-deprotection and renewed acetylation, colchicine (**1**) was obtained (ca. 90% *ee*).

Thus nonracemic colchicine was synthesized in a relatively short reaction sequence. The strength of this synthesis lies in the highly efficient preparation of the key intermediate **202**. However, the overall scheme is stained by the low yield of the key cycloaddition (**205**→**206**, 23%, 45% with respect to 50% recovered starting material).

Cha and co-workers also reported another method for the preparation of the advanced furan intermediate **202** in which they exploited the chiral pool (Scheme 24).[39b] The protected L-serine derivative **210** was converted into the iodide **211**, and its organozinc derivative was treated with the acid chloride **212** in a Pd-catalyzed coupling. The resulting aryl ketone **213** was converted into **214** by benzylic hydrogenation and subsequent iodination at the arene nucleus. A Sonogashira coupling of the acetamide **215** followed by desilylation and reduction with DIBAH afforded the aldehyde **217**. The oxazole **218**, prepared from the aldehyde with TosMIC (**195**), was heated at reflux in *ortho*-dichlorobenzene to yield the same furan **202** previously obtained from the isomeric oxazole **201**.

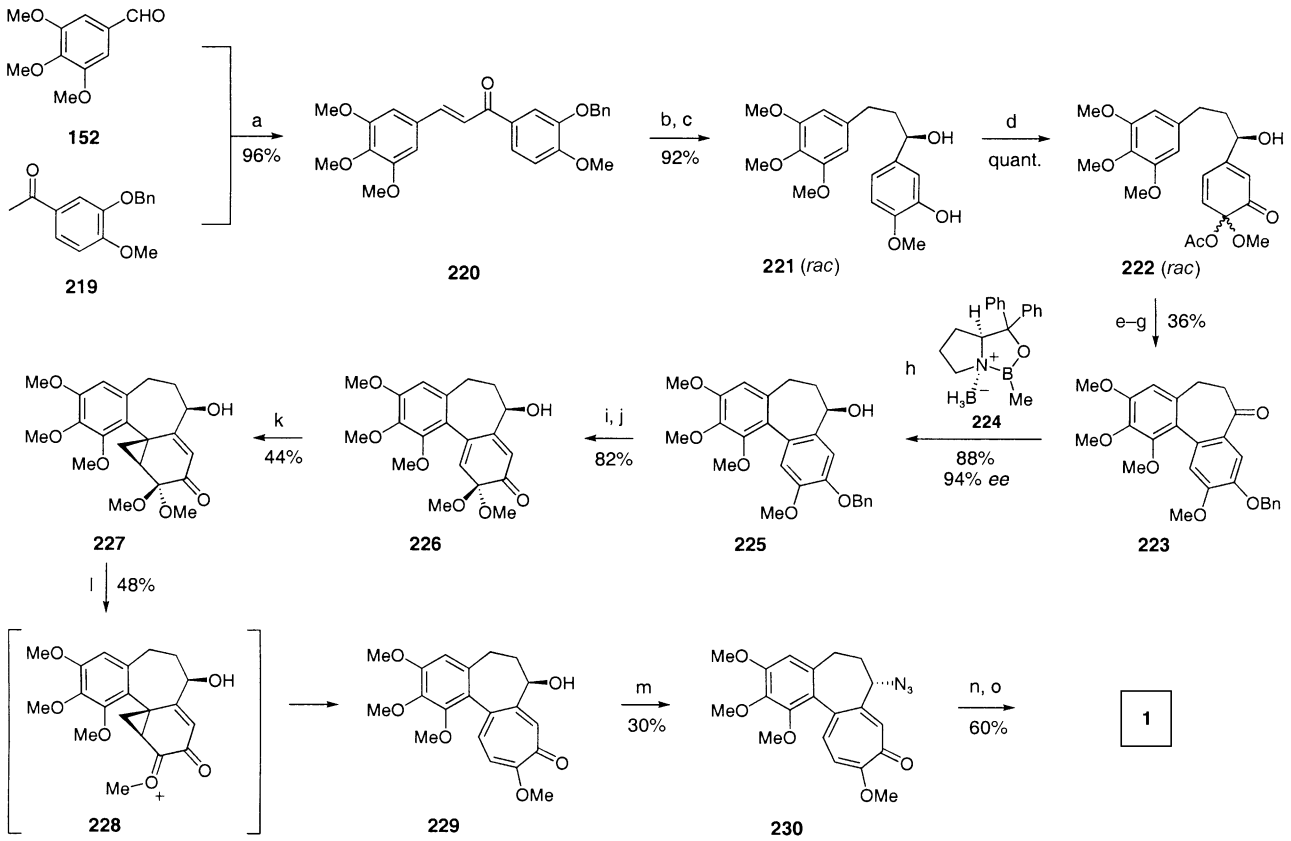
### *4.11. The Banwell Synthesis of (−)-Colchicine by Biomimetic Ring Enlargement*

Another efficient enantioselective synthesis, which is strategically related to the syntheses of Tobinaga and co-workers and Evans et al. and follows the AC′→ABC′→ABC ring enlargement strategy, was reported by Banwell in 1996 (Scheme 25).[38] This synthesis was the culmination of comprehensive efforts by Banwell et al.[38,41,52] and was also guided by the biosynthesis of the natural product, which according to our current knowledge (Scheme 1) does, indeed, proceed




***Scheme 24.*** Alternative route to the colchicine intermediate **202** according to Cha and co-workers. Reagents and conditions: a) MsCl, no further details given; b) NaI, no further details given; c) **211**, Zn/Cu couple, benzene, ultrasound, room temperature, 3 h; then $[Pd(PPh_3)_2Cl_2]$, **212**, ultrasound, 2 h; d) $H_2$ (60 psi), Pd/C, EtOH, $H_2O$, 22 h; e) $I_2$, $Ag(CF_3CO_2)$, $NaHCO_3$, $CHCl_3$, 0 °C, 2 h; f) $CF_3CO_2H$, $Et_2O$, room temperature, 3 h; then $Ac_2O$, $NEt_3$, DMAP, $Et_2O$, 10 h; g) HC≡CTMS, $[Pd(PPh_3)_2Cl_2]$, CuI, $Et_2NH$, DMSO, 90 °C, 15 h; h) $K_2CO_3$, MeOH, room temperature, 11 h; i) DIBAH, $CH_2Cl_2$, −78 °C, 1 h; j) TosMIC, $K_2CO_3$, MeOH, reflux, 1 h; then KOH, reflux, 3 h; k) *o*-dichlorobenzene, reflux, 40 h. Ms = methanesulfonyl; DIBAH = diisobutylaluminum hydride; TosMIC = toluenesulfonylmethylisocyanide.




***Scheme 25.*** Banwell synthesis of (−)-colchicine (**1**). Reagents and conditions: a) NaOH, MeOH, room temperature, 48 h; b) $H_2$, Pd/C, EtOAc, 15 °C, 10 h; c) $NaBH_4$, THF/MeOH, 15 °C, 1.5 h; d) $Pb(OAc)_4$, molecular sieves (3 Å), $CH_2Cl_2$, 15 °C, 1 h; e) $CF_3CO_2H$, molecular sieves (3 Å), THF/benzene, 0 °C, 1 h; f) BnBr, $K_2CO_3$, MeCN, 82 °C, 4 h; g) NMO, TPAP, molecular sieves (4 Å), $CH_2Cl_2$, 15 °C, 43 h; h) **224**, THF, 15 °C, 6 h; i) $H_2$, Pd/C, EtOAc, 15 °C, 9 h; j) $Tl(NO_3)_3$, MeOH, −20 °C, 30 min; k) $Me_3S(O)I$, NaH, DMSO, 15 °C, 7 h; l) $CF_3CO_2H$, $CH_2Cl_2$, 15 °C, 3 h; m) $Zn(N_3)_2{\cdot}Py_2$, DIAD, $PPh_3$, THF, 15 °C, 38 h; n) $PPh_3$, $H_2O$, THF, 15 °C, 63 h; o) $Ac_2O$, pyridine, 15 °C, 15 min. NMO = *N*-methylmorpholine-*N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate.

through ring enlargement of a norcarane intermediate as a precursor for ring C.

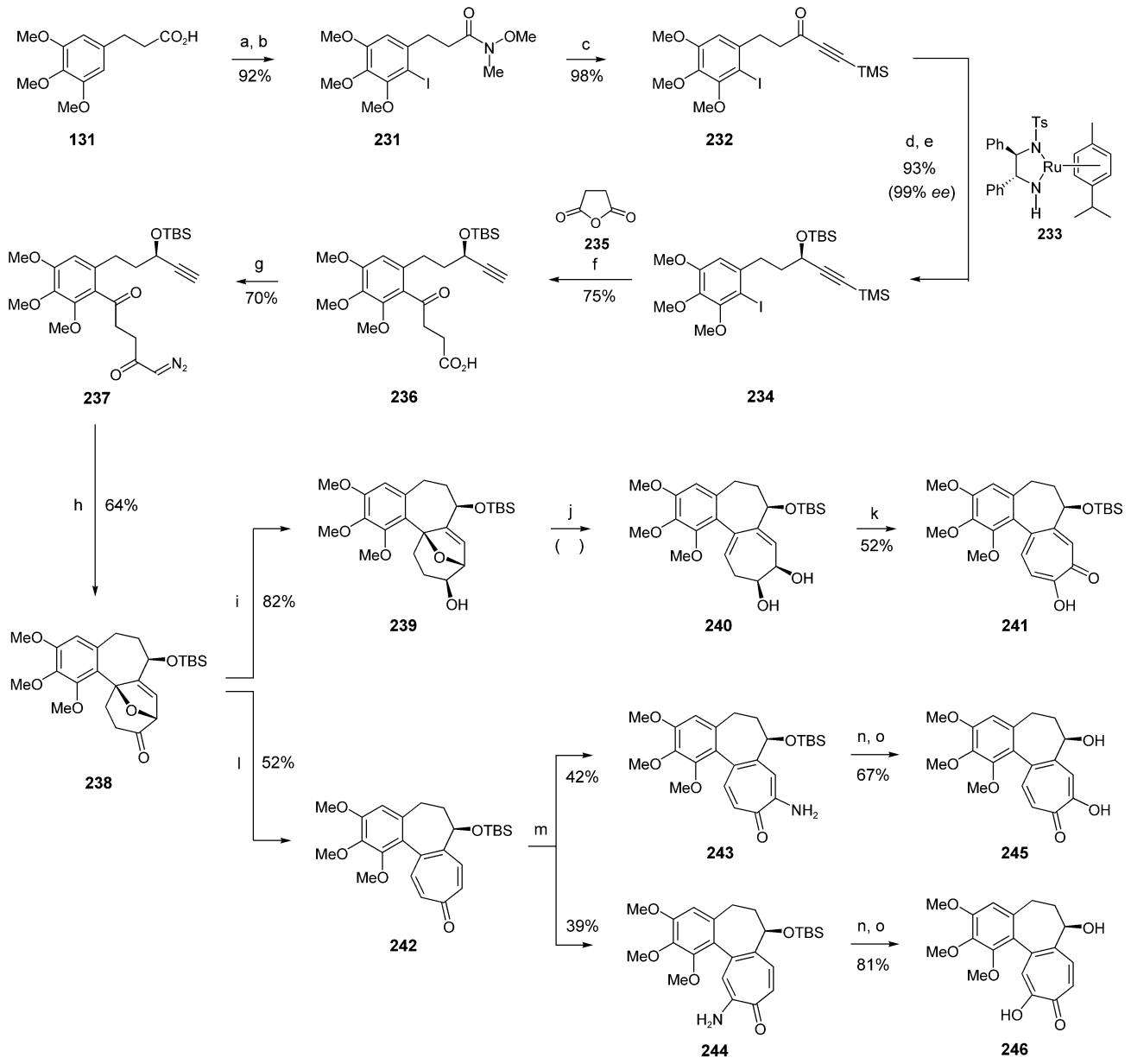
Starting from the easily obtainable chalcone **220**, the stepwise reduction of the C–C double bond and the keto group under cleavage of the benzyl ether afforded the racemic diaryl propanol *rac*-**221**. Wessely oxidation gave rise to the cyclohexadienone *rac*-**222**, which was converted into the aryl ketone **223** by cationic cyclization, benzylation of the resulting phenol, and oxidation of the alcohol. Enantioselective reduction of the ketone **223** with stoichiometric quantities of the CBS reagent **224** afforded **225** (94 % *ee*). Cleavage of the benzyl ether was followed by a renewed oxidation of the phenol, in this case with $Tl(NO_3)_3$ according to the procedure of Taylor and McKillop. Methylenation of **226** with dimethylsulphoxonium methylide gave the cyclopropane **227** in only moderate yield. The ring enlargement to establish the 6,7,7-membered ring system (→**229**) was achieved by treatment of **227** with $CF_3CO_2H$. Along these lines, the tropolone ring C was delivered with the correct oxidation state and arrangement of the oxygen functions as found in the target structure. Unexpectedly, the $S_N2$-type conversion of the OH function of **229** into a nitrogen functionality was rather difficult. At first an azido group was introduced by Mitsunobu reaction. The product **230** was obtained in only low yield, and partial racemization occurred during the subsequent Staudinger reduction. From the resulting amine, the natural product **1** was obtained with only 81 % *ee* after acetylation.

In summary, the synthetic problem was solved by Banwell in a relatively short sequence of rather simple transformations. Even the rather low yields of some steps do not distort the beautiful overall scheme.

### *4.12. Our Synthesis of an Advanced Colchicine Intermediate Exploiting a Rh-Catalyzed Cyclization Cascade*

Our conceptually very direct approach towards colchicin (**1**) is based on a retrosynthetic analysis in which the oxa-bridged key intermediate **238** is traced back to the open-chain cyclization-precursor **237** (A→ABC).[40,53] This strategy was designed in analogy to the benzotropolone synthesis of Friedrichsen and Plüg.[54] The crucial step, a Rh-catalyzed cyclization cascade (**237**→**238**), not only generated the 6,7,7-membered ring system, but also installed the oxygen substituents correctly at C9 and C10 in the newly formed ring C (Scheme 26).

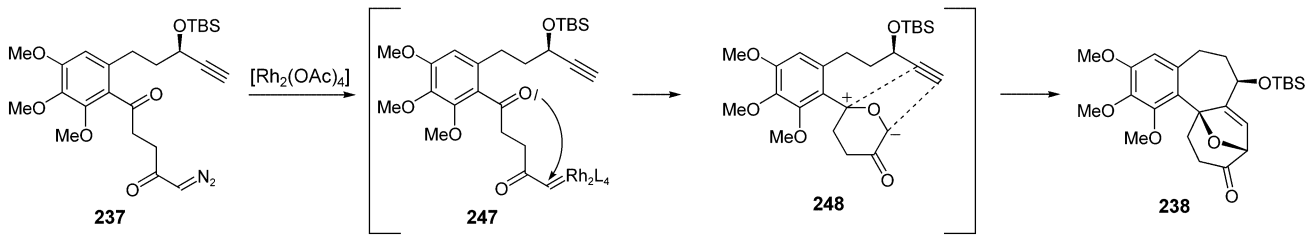
  




***Scheme 26.*** Synthesis of the advanced colchicine intermediates **241** and **245** according to Graening and Schmalz. Reagents and conditions: a) $(COCl)_2$, $CH_2Cl_2$, 0 °C→RT, 12 h; then NHMeOMe·HCl, pyridine, $CH_2Cl_2$, 0 °C, 1 h; b) $Ag(CF_3CO_2)$, $I_2$, $CHCl_3$, room temperature, 4 h; c) LiC≡C-TMS, THF, −78 °C, →−10 °C, 45 min; d) **233** (1 mol %), *i*PrOH, 16 h; e) TBSCl, imidazole, DMF, room temperature, 18 h; f) *i*PrMgCl, THF, −25 °C, 4.5 h; then **235**, THF, −40 °C, 30 min; then $K_2CO_3$, MeOH, room temperature, 3 h; g) *i*BuOCOCl, $NEt_3$, THF/$Et_2O$, −20→−15 °C; then $CH_2N_2$, $Et_2O$, −5 °C, 16 h; h) $[Rh_2(OAc)_4]$, toluene, reflux, 4 h; i) L-selectride, THF, −78 °C, 3 h; j) TMSOTf, $NEt_3$, $CH_2Cl_2$, −50→−10 °C, 1 h; then $K_2CO_3$, MeOH, 0 °C, 45 min; k) DMSO, $(CF_3CO)_2O$, $CH_2Cl_2$, −60 °C, 1.5 h; then $NEt_3$, −60 °C, 1.5 h; l) $Et_2AlCl$, $CH_2Cl_2$, −78→0 °C, 2.5 h; m) $NH_2N_2·H_2O$, EtOH, 0 °C→RT, 4.5 h; n) TBAF, THF, 0 °C, 45 min; o) 2 N KOH, EtOH, 110 °C, 16 h. TBS = *tert*-butyldimethylsilyl.

The bifunctional Weinreb amide **231** was prepared from hydrocinnamic acid **131** and treated with lithium trimethylsilylacetylide to give the alkynone **232**. This compound proved to be an excellent substrate for enantioselective transfer hydrogenation according to Noyori. In the presence of the Ru complex **233** as a catalyst, the corresponding propargylic alcohol was obtained in essentially enantiomerically pure form and was subsequently silylated to give the protected derivative **234** in 93 % yield (two steps). Acylation to give the ketocarboxylic acid **236** was achieved utilizing a protocol of Knochel for iodine–magnesium exchange and reaction of the resulting Grignard intermediate with succinic anhydride (**235**). An advantage of this method was that deprotonation at the propargylic position, which was observed with the stronger base *n*BuLi, could be inhibited. Treatment of the α-diazoketone **237** (obtained from **236**) with catalytic $[Rh_2(OAc)_4]$ in refluxing toluene gave the tetracyclic key intermediate **238** with complete diastereoselectivity.

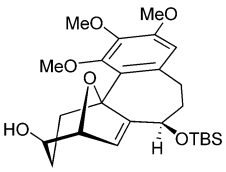



***Scheme 27.*** Rh-Catalyzed cyclization cascade to the key intermediate **238**.

The mechanism and scope of related transformations introduced by Ibata[55a] were investigated in detail by Padwa et al.[55b] As shown in Scheme 27 the cyclization cascade is initiated by the generation of an electrophilic rhodium carbene **247**, which is then attacked by the adjacent Lewis basic carbonyl group to form a reactive carbonyl ylide **248**. The ylide is trapped in another intramolecular reaction step, a 1,3-dipolar cycloaddition with the tethered alkyne unit.

The cycloaddition product **238** formed in 64 % yield has a rather rigid ring system in which the benzylic C–O bond is aligned with the π system of the aromatic ring. Therefore, a selective cleavage of the oxa bridge should be feasible by exploiting stereoelectronic effects.

In fact, the alcohol **239**, prepared from **238** by reduction with L-selectride, is readily converted into the dienediol **240** upon treatment with $TMSOTf/NEt_3$ and immediate hydrolysis of the primarily formed bis(silyl ether) (to avoid isomerization by a sigmatropic [1,5] H-shift). Oxidation of **240** with $DMSO/(CF_3CO_2)_2O$ then immediately gave rise to the stable tropolone **241**. An alternative route for the conversion of the key intermediate **238** into a tropolone started with its Lewis acid mediated dehydration to the tropone **242**. Following a similar protocol as applied by Boger, treatment of **242** with hydrazine resulted in the formation of the two regioisomeric aminotropones **243** and **244**, which were easily separable. From these, the two regioisomeric tropolones **245** and **246**, respectively, were accessible by desilylation and alkaline hydrolysis. As **241** and **245** can be converted into the Banwell intermediate **229**, their formation completes a formal total synthesis of colchicine (**1**). Furthermore, the alternative route via the tropone **242** opens an easy entry to the pseudo-colchicine series starting from **246**.




**239**

With a 12 % overall yield for the conversion of the simple starting material **131** into the advanced colchicine precursor **241**, our synthesis represents a highly efficient approach towards colchicinoid structures (Scheme 26). The strategy should be flexible enough to allow the synthesis of modified analogues. However, this has to be demonstrated in the future.

## 5. Summary

Over the past 50 years, colchicine has challenged synthetic chemists like only few other target molecules. The synthetic efforts of many research groups have culminated in fascinating and very diverse synthetic solutions (Table 1). These studies led to the development of novel tropolone syntheses and served to scrutinize the methodology for the synthesis of seven-membered rings in general. Although the early syntheses represent cultural achievements of highest merit, their

***Table 1:*** Summary of colchicine syntheses.[a]

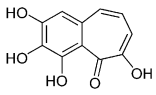
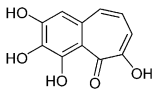
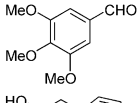
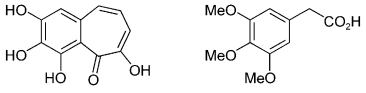
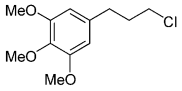
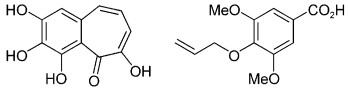
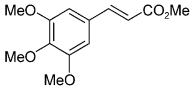
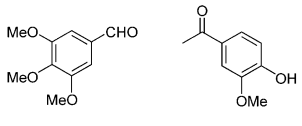
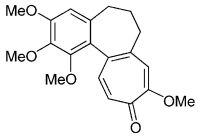
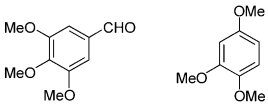
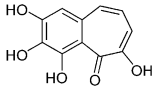
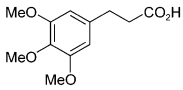
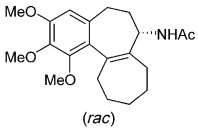
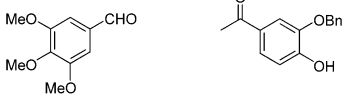
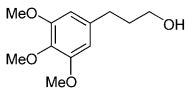
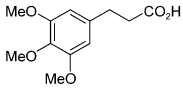
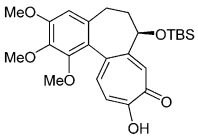
| Authors | Year | Starting compound | Target | Number of steps | Yield [%] |
|---|---|---|---|---|---|
| Eschenmoser and co-workers | 1959 |  | (±)-colchicine (*rac*-**1**) | 22 | 0.00006 |
| van Tamelen et al. | 1959 |  | Trimethylcolchicinic acid (*rac*-**25**) | 18 | 0.0005 |
| Nakamura et al. | 1962 |  | (±)-colchiceine (*rac*-**21**) | 20 | 0.0007[b] |
| Woodward | 1963 |  | (±)-colchiceine (*rac*-**21**) | 23 | –[c] |
| Scott et al. | 1965 |  | desacetamidocolchiceine (**24**) | 11 | 0.1 |

*Table 1:* (Continued)

| Authors | Year | Starting compound | Target | Number of steps | Yield [%] |
|---|---|---|---|---|---|
| Toromanoff and co-workers | 1965 |  | desacetamidocolchiceine (**24**) | 15[d] | 0.3[d] |
| Kaneko et al. | 1968 |  | desacetamidocolchiceine (**24**) | 11 | 0.5[e] |
| Kato et al. | 1974 |  | desacetamidocolchiceine (**24**) | 9 | ~1 |
| Tobinaga and co-workers | 1974 |  |  | 7 | 24 |
| Evans et al. | 1984 |  | trimethylcolchicinic acid (*rac*-**25**) | 12 | 5 |
| Boger and Brotherton | 1985 |  | desacetamidocolchiceine (**24**) | 10[f] | 3.5[f] |
| Wenkert et al. | 1989 |  |  (*rac*) | 10 | 6.3 |
| Banwell | 1996 |  | (−)-colchicine (**1**) ~81% *ee* | 15 | 0.9 |
| Cha and co-workers | 1998 |  | (−)-colchicine (**1**) ~90% *ee* | 18 | 1.9 |
| Graening and Schmalz | 2004 |  |  | 11 | 12 |

[a] The overall yields and the number of steps, as a matter of interpretation, should only be taken for the purposes of comparison. [b] For the racemic series. [c] No yields were reported. [d] For the shorter and more efficient route via **94**. [e] Based on the yields for **26**→**35** reported by Scott et al. [f] Based on the preparation of pyrone **54** reported by Eschenmoser and co-workers.

overall efficiency, of course, cannot meet modern standards. As the comparative analysis of the many syntheses reveals, solutions for the problem have only slowly evolved and colchicine must still be considered as a difficult target molecule. Notwithstanding the powerful arsenal of modern synthetic technology, even today synthetic chemists require a high level of creativity and the ability to integrate subtle structural and reactivity aspects to tame such a recalcitrant target structure.

Like other tubulin-binding molecules such as taxol and the epothilones, colchicine enjoys a great interest from medicinal research and has experienced a renaissance in the last few years. To explore its pharmaceutical potential further as a lead structure, flexible synthetic schemes must be developed that allow a diversity-oriented synthesis of structural analogues of colchicine. Only the most recent syntheses come within reach of the efficiency and flexibility levels required for such purposes. Consequently, it can be expected that colchicine will remain an important synthetic target and challenge further creativity in synthetic chemistry.

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