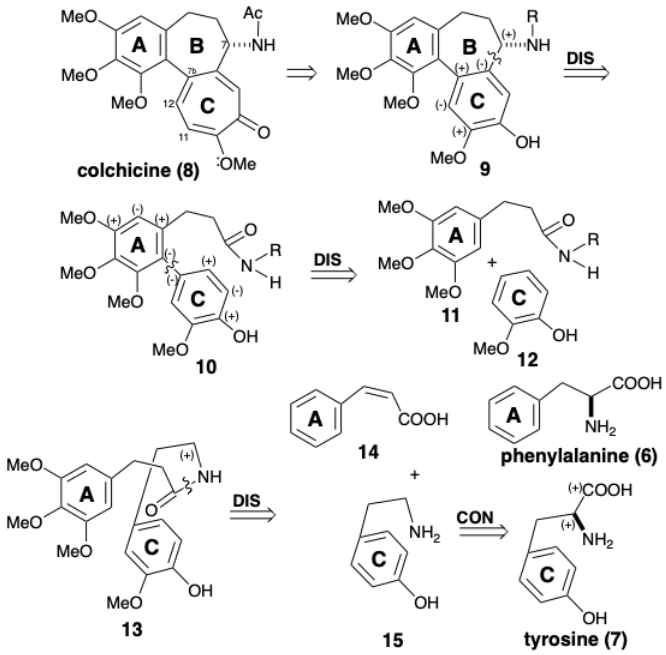
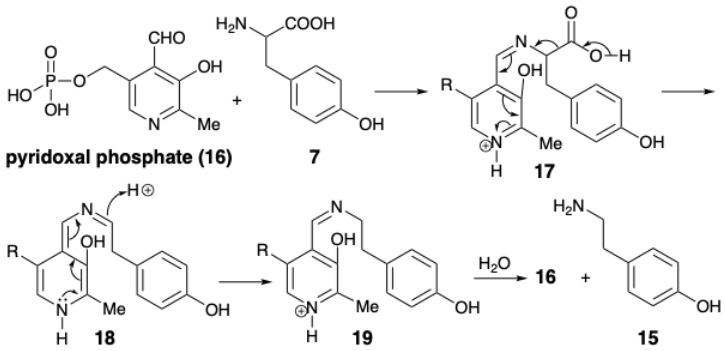
6.1: Colchicine

Biosynthetic Strategy

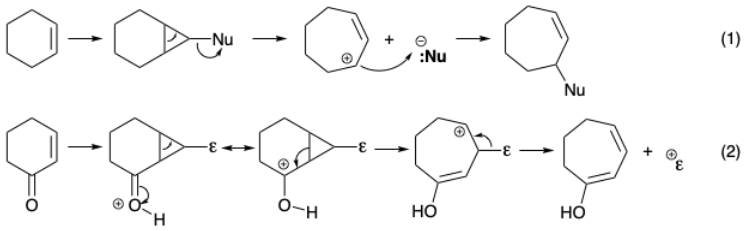
The use of aromatic amino acids, i.e. phenylalanine or tyrosine, as the sole starting materials for colchicine (**8**) requires preparing the seven-membered C-ring by expansion of an aromatic six-membered ring in a precursor such as **9**. How the ring expansion is accomplished will considered later. Since the starting amino acids do not have benzylic amino groups, it is likely that the bond between the C ring and the benzylic carbon is formed by electrophilic aromatic substitution. Since the starting amino acids are aryl propionic acid derivatives, the electrophile could be derived from an aryl propionic amide such as **10**. Clearly the bond between the A and C rings in **10** would be formed by oxidative coupling of electron rich aryl precursors **11** and **12**. Since the nitrogen in **11** probably comes from an amino group in the C ring amino acid precursor, and since **12** should also be derived from an a-amino arylpropionic acid, it is likely that the structure **12** must be revised so that the R group in **11** incorporates **12** as in the amide **13** (see below). A cinnamic acid **14**, generated by elimination of ammonia from phenylalanine (**6**) could be the progenitor of the arylpropionic acid portion of the amide **13**.



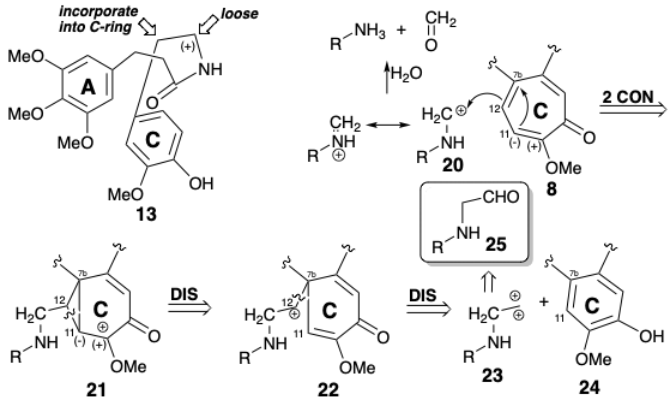
Generation of a phenylethyl amine **15** by decarboxylation of tyrosine (**7**) requires cleavage of a bond lying on a dissonant circuit. Such a cleavage is achieved biosynthetically by a polar process which converts the amino group temporarily into a derivative that can stabilize electronic excess on the amino carbon. The decarboxylation of tyrosine (**7**) to give p-hydroxy-b-phenthyl amine (**15**) is an example of a general reaction of amino acids that is promoted by the coenzyme pyridoxal phosphate (**16**). The process is initiated by the formation of a Schiff base **17**. The pyridine nitrogen is conjugated with the carbon a to the carboxyl and can stabilize electronic excess at that carbon. The imine nitrogen does not provide polar activation; it serves merely as a linking atom. Schiff base **17** readily undergoes acid catalyzed decarboxylation to form **18**. Protonation of **181** leads to rearomatization delivering the Schiff base **19.** Hydrolysis delivers the phenylethyl amine **15** and regenerates **16**. Thus, *pyridoxal phosphate (16) acts as a polar reactivity-inverting catalyst.*



We encountered polar ring expansion strategies in the total synthesis of longifolene (see section 4.4). There, a fused bicyclic intermediate, generated by cyclopropanation of a cyclohexene, underwent cleavage of the fusion bond in conjunction with departure of a nucleofuge to deliver a cycloheptenyl array (eq 1). An analogous process, involving departure of an electrofuge in conjunction with cleavage of the fusion bond in a similar intermediate, depends on a cyclopropyl carbinyl to homoallyl carbocation rearrangement (eq 2). The presence of oxygen substituents in the colchicine C ring suggests the possibility that such a ring expansion mechanism may transpire during the biosynthetic conversion of a six-membered C ring precursor into the seven-membered C ring.



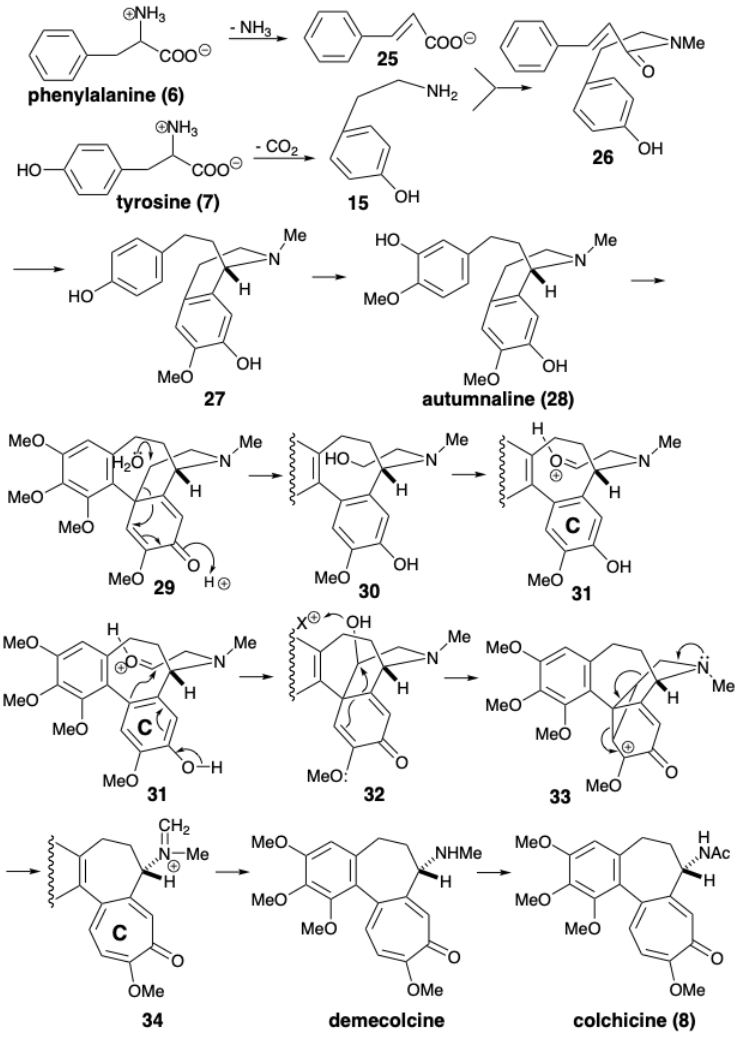
One carbon of the phenethyl sidechain in **13**, the benzylic carbon, could be incorporated in an aromatic precursor to generate the seven-membered C ring. The remaining carbon of the sidechain must be disconnected. Disconnection of this carbon as a carbocation can be stabilized by the amino group as in **20**. Retrosynthetic analysis of the colchicine biosynthetic ring expansion, presuming **20** as electrofuge, suggests cyclopropyl carbinyl and homoallyl carbocation intermediates **21** and **22**. The carbon that is inserted into the aromatic ring of the starting material **24** corresponds to the dication synthon **23** for which an aldehyde might serve as a synthetic equivalent.



Biosynthesis

In the biosynthesis of colchicine (**8**), NH_3 is eliminated from phenylalanine (**6**), and tyrosine (**7**) is decarboxylated, before an amide **26** is formed by joining the resulting intermediates **25** and **15**. The seven-membered B ring is created by an enantioselective intramolecular electrophilic aromatic substitution that gives **27** and an oxidative coupling of **28** that delivers **29**. Functionalization of an apparently unactivated methylene in **29** is accomplished by a sequence involving polar hydrolytic fragmentation to **30** followed by oxidation to an aldehyde suitable for insertion into the six-membered C ring progenitor in **31**. Expansion of the aryl ring to generate a seven-membered tropolone is initiated by intramolecular electrophilic aromatic substitution. Intramolecular

alkylation of **32** followed by a fragmentation of an intermediate cyclopropane **33** produces the ring expanded skeleton in **34** of the biosynthetic target. Final hydrolysis of the imminium group, N-demethylation and N-acetylation delivers colchicine (**8**).



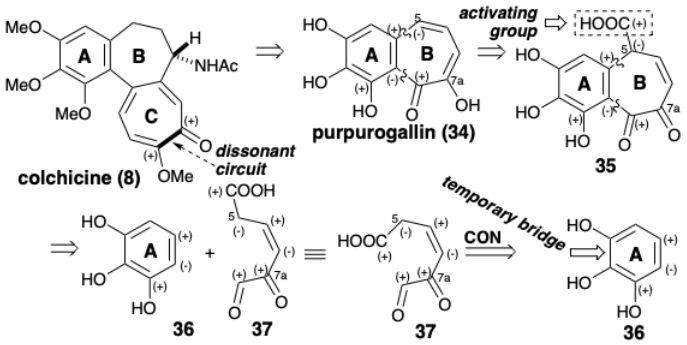
Molecular Characteristics

The stability of aromatic derivatives is often exploited in synthesis by strategies that incorporate preformed aromatic moieties. Thus, in the biosynthesis of colchicine (**8**), the aromatic A-ring is derived from the preformed aromatic ring of phenylalanine (**6**). The four different total syntheses of colchicine to be considered in this section all adopt this same strategy. In contrast with the biosynthesis, however, the total syntheses all employ fully functionalized aromatic starting materials. This is because the *regioselective* hydroxylations, that are acheived enzymatically in the biosynthesis, are not so readily achieved in the laboratory.

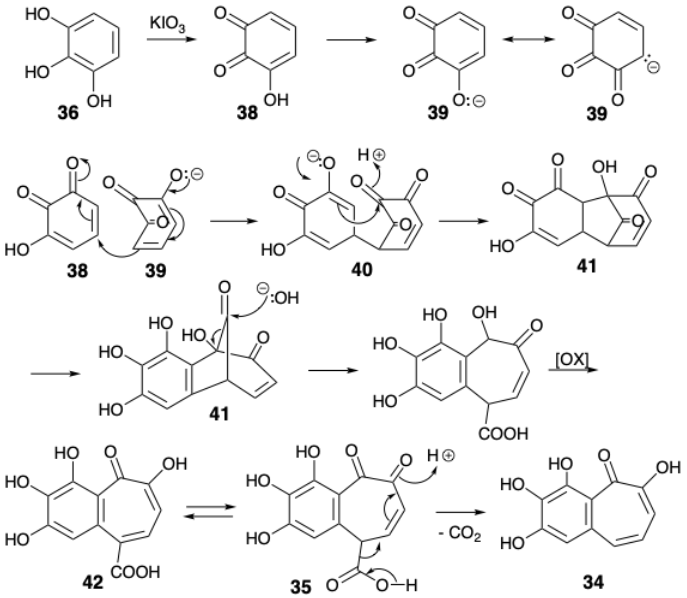
It should also be noted that the C ring of colchicine (**8**) contains two functional groups that provide electrophilic activation on adjacent carbon atoms, a polar reactivity dissonance. Thus, these functional groups cannot be exploited directly in a polar reaction (i.e. without umpölung) to create the C-C bond of the dissonant circuit between these carbon atoms. In each of the following syntheses, the seven- membered C ring is added to an AB-ring precursor. In each case, a different strategy is exploited for annelation of the C ring.

Key Intermediate-Directed Strategies for Conchicine

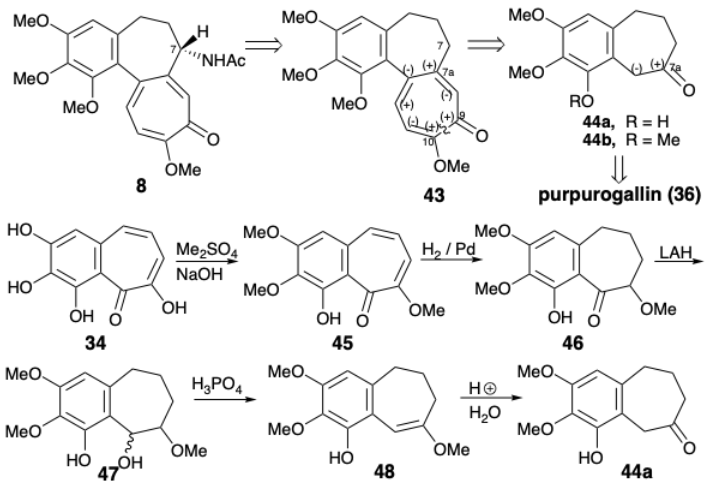
Two syntheses of colchicine exploited a readily available key intermediate, purpurogallin (**34**), for the AB ring moiety of **8** and formed the seven-membered C-ring by *nonpolar* reactions. Polar reactivity analysis of **34** suggests a synthesis from an aromatic precursor **36**. Thus, appendage to **36** of the B-ring in **34** can be facilitated by addition of an activating carboxyl as in **35** that could be generated from **36** and **37** by two polar bond-forming reactions. In fact, the aromatic starting material **36** can also be the precursor of a temporarily-bridged synthetic equivalent **39** (*vide infra*) of the synthon **37**.



Purpurogallin (**34**) was a well-known product from the oxidation of pyrogallol (**36**). It is probably formed by dimerization of 3-hydroxy-o-quinone (**38**). An initial Michael addition of the enolate **39** to **38** to give **40** followed by an intramolecular aldol condensation leads to a tricyclic intermediate **41** (see below). This is cleaved in a retro Dieckman reaction, typical for β-diketones, to produce a bicyclic carboxylic acid **37**, which can be isolated. This vinylogous β-keto acid readily undergoes decarboxylation to deliver **28**.

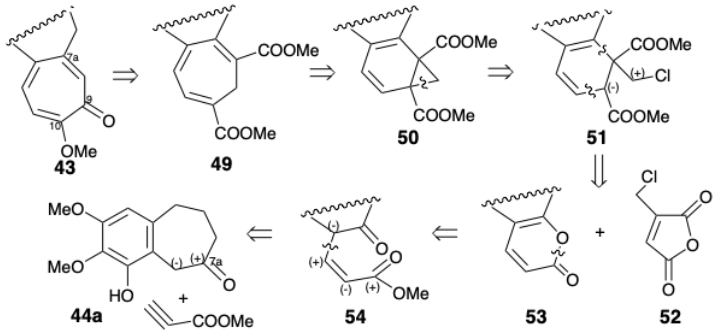


Both syntheses employing **34** for the A and B rings simplified the target by neglecting the acetamido group. This could be introduced by benzylic oxidation after completion of the carbon skeleton of the target **8**. Both syntheses construct the simplified target **43** from benzosuberone derivative **44**, in which the carbonyl functional group provides activation for annelation of the C ring. Eschenmosher[1] prepared **39a** by reducing the trimethyl ether **45** of purpurogallin (**34**) via **46**, **47**, and **48**.

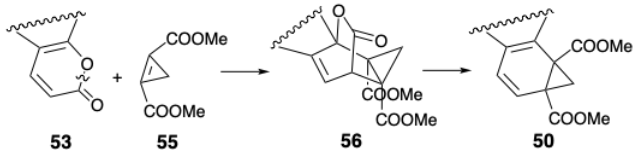


A Cycloaddition-Pericyclic Rearrangement Strategy for the C Ring

Eschenmosher's strategy[1] for annelation of the seven membered ring C was to build a diene onto **44a**, then construct a six membered carbocycle by a Diels-Alder reaction of the diene and finally expand the six to a seven membered ring by pericyclic rearrangement of a norcaradiene. Facile interconversion of cycloheptatrienes such as **49** with norcaradienes such as **50** is a well-known [3.3] sigmatropic (Cope) rearrangement that is driven to favor cycloheptatrienes by the relief of ring strain associated with cleavage of the cyclopropane. It is *doubtful that the strategy was concieved by rigorous retrosynthetic analysis* since conversion of **49** to **43** would certainly require extensive functional group manipulations. The decision to employ **49** as a precursor for **43** almost certainly evolved as a consequence of the decisions to employ: (1) a Cope rearrangement of a norcaradiene.

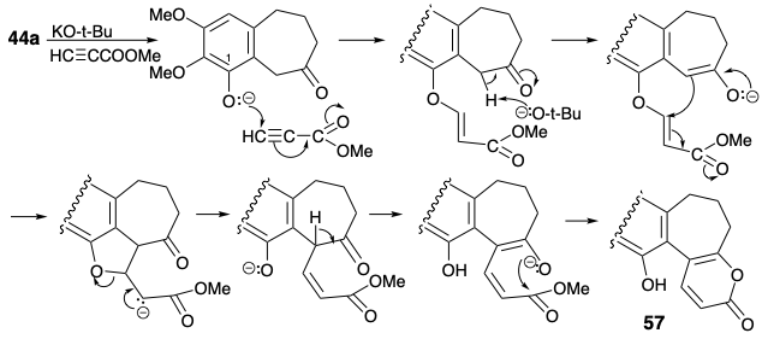


Therefore, chloromethylmaleic anhydride (**52**) is ideally suited to cycloadd to the reletively electron rich diene **53**. Perhaps a more obvious dislocation of **50** would be to **53** and the cyclopropene **55**. This branch of the retrosynthetic tree would, most probably, be considered first because it would provide a more convergent synthesis. Thus, reaction of **55** with α-pyrone **53** would deliver **50** directly by a Diels alder cycloaddition, followed *in situ* by a retro Diels Alder cycloelimination of carbon dioxide from an intermediate **56**.

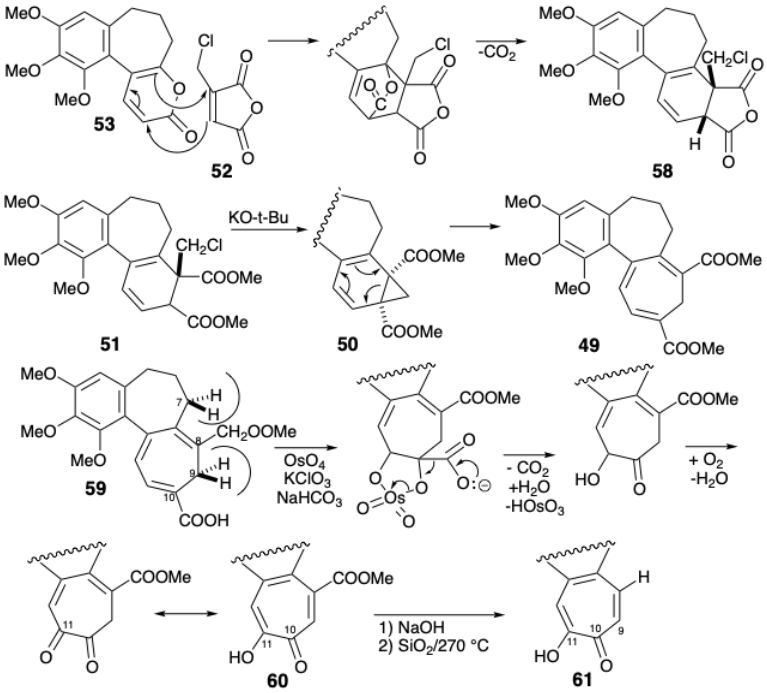


The alternative precursor, dienophile **52** with a chloromethyl substituent, is suggested by polar disconnection of **50** to **51** that can be derived from **53** by a Diels-Alder-retro Diels-Alder sequence. Dienophile **52** rather than **55** was chosen because it is more readily available than **55**. A Diels-Alder addition of **52** to **53** followed by a retro Diels-Alder elimination of CO_2 from an intermediate adduct, a carbonyl-alkene exchange process, will provide the cyclohexadiene **51**. The driving force for the process is the generation of a relatively stable C=O bond in exchange for the C=C bond of the dienophile **52**. The diene **53** is an enol lactone derivable from the acid **54**. Polar analysis of **54** suggests construction from **44a** and methyl propiolate by a polar 1,4-addition. Apparent Michael alkylation of **44a** with methyl propiolate provided pyrone **57**. Though **44a** could give **57** via direct Michael

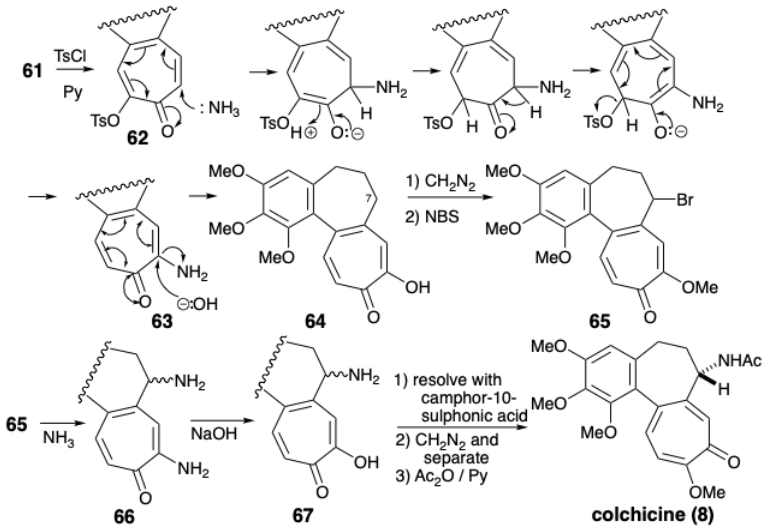
addition to the yneone, in fact the reaction was more complex. It involved participation by the phenolate anion. Thus, the electrophile was delivered intramolecularly to the rather hindered benzylic carbon of **44a**.



After methylation of phenol **57**, the annelation of a cyclohexadiene **58** was achieved by the well- known cycloaddition-cycloelimination reaction of α-pyrones. Base-catalyzed intramolecular alkylation of the diester **51** from **58** led, via the norcaradiene **50**, to the cycloheptatriene **49**. The least hindered ester in **49** was readily hydrolyzed selectively, and the resulting acid afforded a tropolone **61** via osmium catalyzed vicinal hydroxylation-decarboxylation, saponification of the remaining ester in **60** and a second decarboxylation.

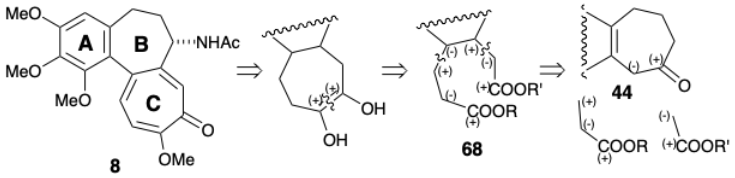


Unfortunately, the sequence leads to an oxygen function on C-11 rather than C-9 as required for colchicine. Transposition of the functional group was achieved by a well-precedented sequence of nucleophilic displacements on the tosylate derivative **62** of **61** first with NH_3 to give **63** then with -OH to deliver **64**. The tropolone **64** was then methylated and functionalized at C-7 by allylic bromination with N-bromosuccinimide to provide **65**. Nucleophilic displace-ment of bromide by ammonia gave the required C-7 amine accompanied by ammonolysis of the tropolone, a vinylogous ester. Saponification of the resulting vinylogous amide **66** gave **67**, that afforded colchicine upon methylation and acetylation.

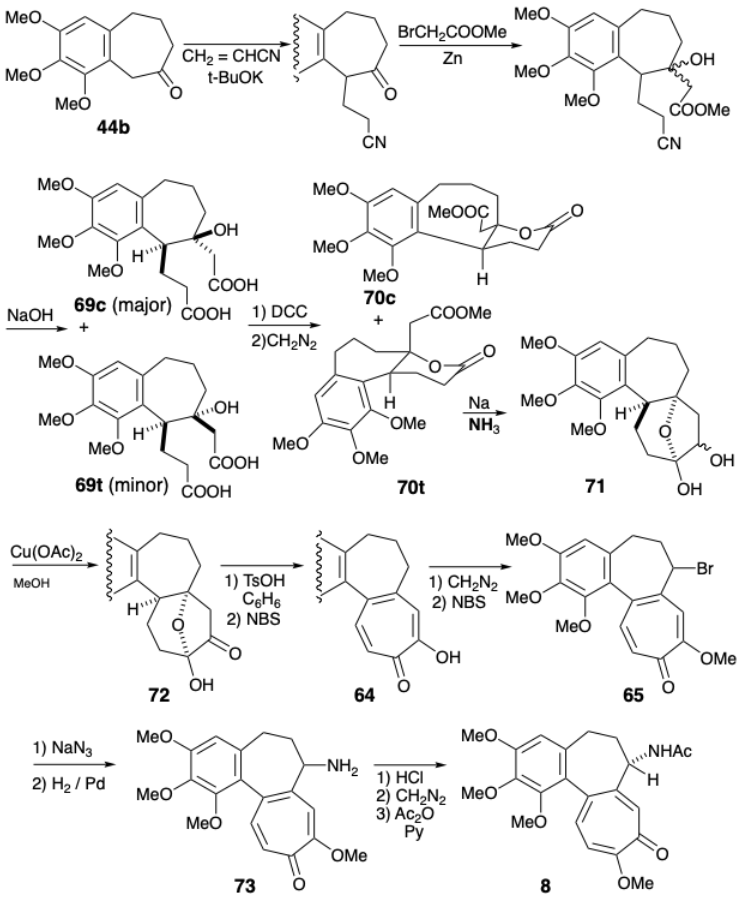


An Acyloin Strategy for the C Ring

Van Tamelen's strategy for annelation of the C-ring with vicinal oxygen functionality recognizes the applicability of an intramolecular acyloin reaction for creation of the dissonant circuit between vicinal electrophilic activating groups.[2] Further polar analysis suggests a synthesis of the requisite diester intermediate **68** by exploiting the polar activation provided by a carbonyl group in an AB-ring precursor **44**. Thus, appendage of acetic and a propionic acid side chains should be feasible respectively by a Reformatsky reaction and Michael alkylation.



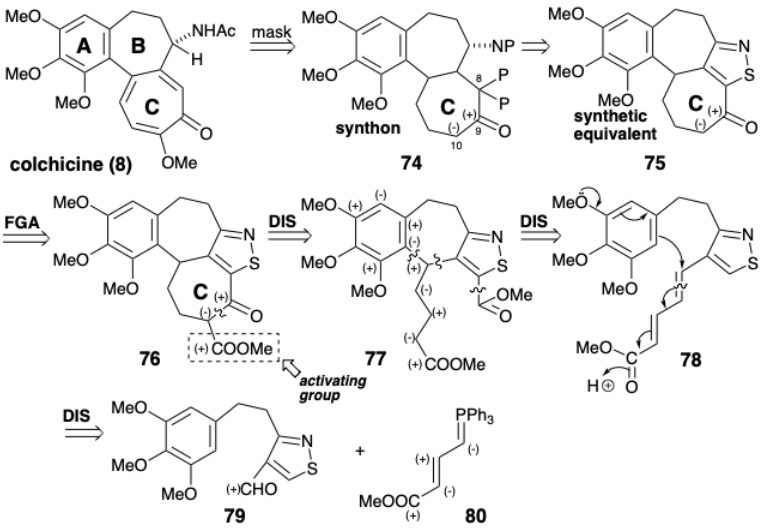
A pair of isomeric hydroxy diacids **69c** and **69t** was obtained by Michael alkylation of **44b** with acrylonitrile, Reformatsky reaction of the intermediate ketonitrile and hydrolysis. The hydroxyl group was masked intramolecularly as a lactone, and the remaining carboxyl group was methylated. Only one of the isomeric lactone esters **70** underwent an acyloin reaction which provided **71**. Unfortunately, this was the minor isomer **70t**, with an axial carbometh-oxymethyl substituent. The ester groups in the major isomer **70c** could not readily attain juxtaposition suitable for intramolecular acyloin reaction. The acyloin product **71** was oxidized to **72** with Cu(II) and further oxidized with NBS to provide tropolone **64.** Methylation and bromination delivered the bromide **65,** an intermediate also prepared by Eschenmosher. Substitution of an amino group for the bromo substituent in **65** followed by hydrolysis, remethylation of the vinylogous carboxylic acid, and N-acetylation produced colchicine **8**.



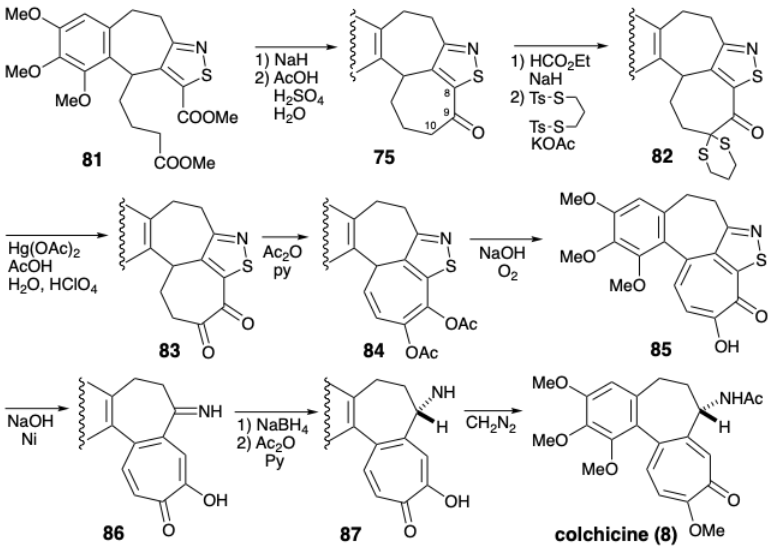
Extensive functional group manipulations after completion of the carbon skeleton were required in the Eschenmosher synthesis because an annelation strategy for the C ring was adopted that ignored target related functionality. Van Tamelen could complete his synthesis with less functional group manipulations because more target related functionality, that had been exploited to facilitate skeletal construction, was present after completion of the C ring.

A Target-related Functionality-promoted Polar Bond Formation Strategy

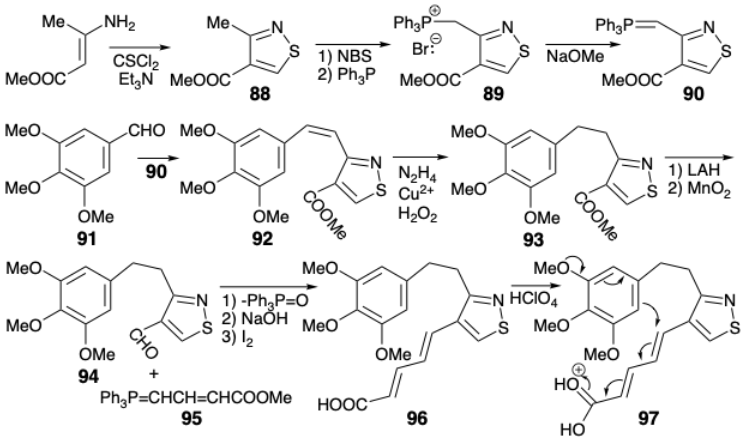
Another synthesis of colchicine (**8**), also involving annelation of ring C on a preformed AB-ring intermediate, was devised by R. B. Woodward.[3] The strategy is unique in incorporating the 7-amino substituent early and in its extensive use of target related functionality to facilitate carbon skeletal construction. Dislocation of the target **8** to derivative **74** in which the 8-position is also blocked allows selective introduction of oxygen at C-10. In the synthetic equivalent **75** of the synthon **74**, an *aromatic* isothiazole ring masks both the amino substituent and C-8. Annelation of the C-ring can be achieved by a Dieckman cyclization **77** → **76** exploiting the polar activation provided by the C-9 carbonyl and an activating carbomethoxyl group appended to C-10 in a precursor **77**. The polar activation provided by this carbomethyl group in **77** suggests an electrophilic aromatic substitution **78** → **77** for annelation of the B- ring. Of course, for the appropriate electrophilicity to be expressed, the carbomethoxyl group in **77** must be conjugated with the γ-position as in **78**. The isothiazole also serves as a temporary bridge in **78**, that assists entropically in the **78** → **77** cyclization. The carbomethoxyl in **78** also allows a polar elaboration of the dienoic ester array from an isothiazole aldehyde precursor **79** by stabilizing a carbanion in the ylide fragment **80**. The sulfur atom in the isothiazole ring even provides activation for carbanion generation a to sulfur in **78** allowing polar connection of the carbomethoxyl required in **77**. The extensive strategic utilization of the isothiazole unit in Woodward's strategy is a hallmark of this synthetic plan.



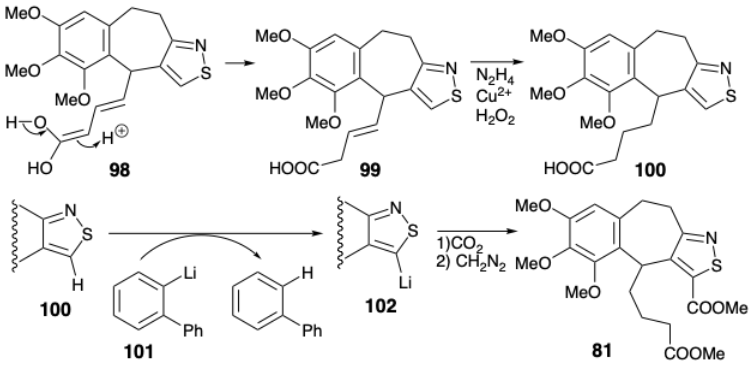
After Dieckman cyclization of **81**, the C-9 monoketone **75** is selectively oxidized at the C-10 by a polar reaction exploiting the nucleophilic activation at C-10 provided by the C-9 carbonyl group. Nucleophilic attack by the C-10 carbanion on a sulfur electrophile leads to oxidation of C-10 (and concomitant reduction of sulfur). The resulting thioketal **82** is hydrolyzed to **83**, that affords the enol acetylation product **84**. The enediolate obtained by saponification of the diacetate **84** is readily oxidized to deliver **85**. Desulfurization of **85** with Raney nickel removes the isothiazole masking group. Reduction of the resulting imine **86** followed by acetylation provides **87** that is N-methyl-ated to deliver colchicine (**8**).



Woodward's synthesis of the key intermediate **81** is centered around the novel aromatic isothiazole ring. The starting material, an isothiazole **88,** is readily available from methyl β-aminocrotonate, an enamine derived from methyl acetoacetate. The conjugated methyl group in **88** is readily brominated with NBS. Alkylation of Ph_3P affords a phosphonium bromide **89**, that gives ylide **90** upon deprotonation. Wittig olefination of 3,4,5-trimethoxybenzaldehyde (**91**) with ylide **90** produces alkene **92** that was selectively hydrogenated with diimide. Catalytic hydrogenation of **92** was precluded by the susceptibility of the isothiazole ring to hydrogenolysis. Hydride reduction of the ester **93** and partial oxidation of an intermediate conjugated carbinol gave the aldehyde **94**. Wittig olefination of **94** with ylide **95** followed by saponification and cis-trans isomerization provided **96**.

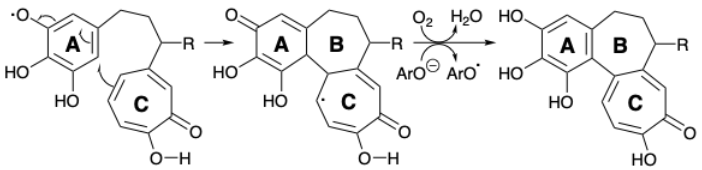


This diene underwent intramolecular electrophilic aromatic substitution upon treatment with perchloric acid. The temporary bridge provided by the isothiazole ring undoubtedly facilitates this cyclization by favorably juxtaposing the reacting carbon centers. Selective reduction of the cyclization product **99** with diimide gave **100**. The final carbon required for the C ring was introduced by carbonylation of an organolithium derivative **102** from the thiazole **100**. Thus, selective metallation in the presence of a carboxylate was achieved with the relatively non nucleophilic, sterically encumbered aryl lithium **101**. The lithiated thiazole **102** gave the key intermediate **81** upon carbonation followed by methylation.

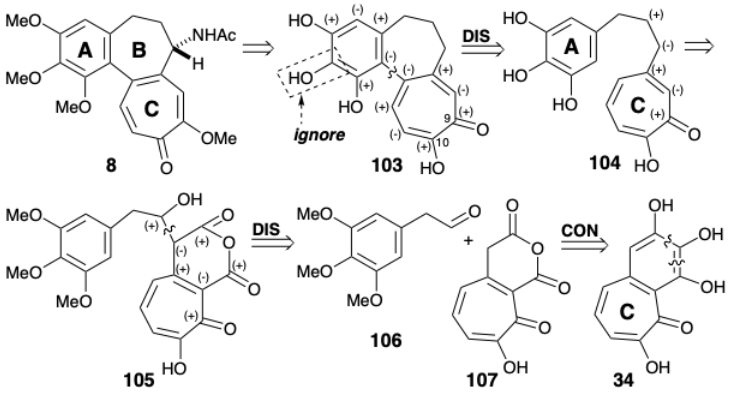


A Hypothetically Biomimetic Strategy

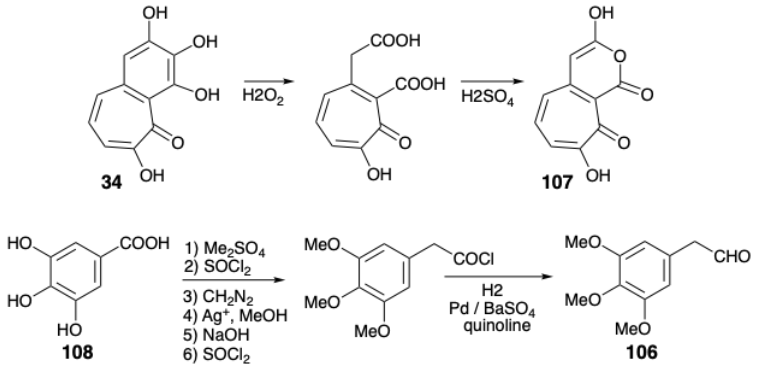
A fourth synthesis of colchicine, devised by Scott[4], differs from the previous three in its strategy for skeletal constuction. Scott assembled an intermediate containing the A and C rings and then created the B ring by an intramolecular oxidative coupling. This strategy was based on a hypothetical mechanism for colchicine biosynthesis, that is now know not to be operative. In this mechanism, in contrast with the actual biosynthetic mechanism (see above), generation of a tropolone C-ring by ring expansion of an aromatic precursor preceeds the oxidative coupling that creates the B-ring.



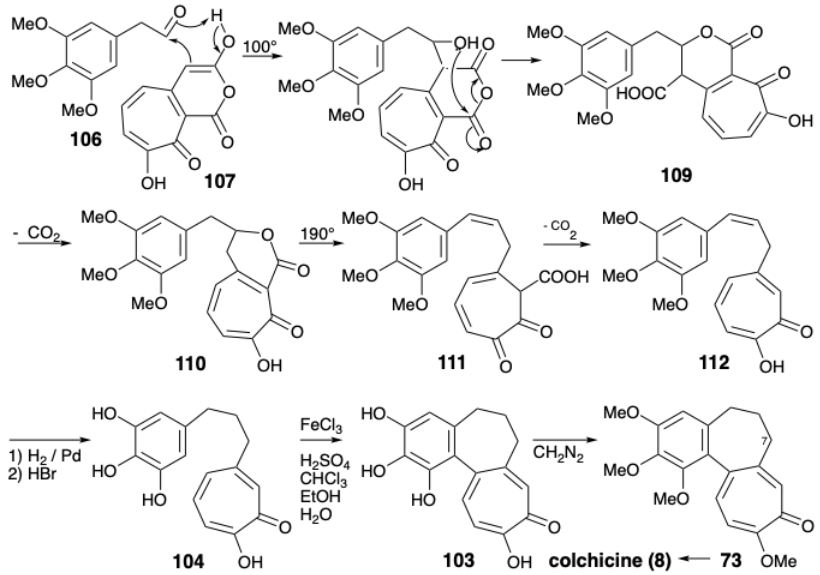
The tactic of introducing the colchicine amino group at the end of the synthesis was well-precedented. Thus, the Scott strategy begins with dislocation of the target **8** to a precursor **103**. The bond between aryl and tropolone rings lies along a dissonant circuit between the oxygen functionality at positions 1 + 9, 1 + 10, 3 + 9, or 3 + 10. Thus, polar analysis reveals that formation of this bond cannot be achieved by a polar process using these functional groups to provide activation since union of two nucleophilic centers would be required. Such a process can be achieved oxidatively, suggesting dislocation of **103** to a precursor **104** with two monocyclics joined by a simple trimethylene bridge. The polar reactivity afforded by the carbonyl group in **104** can be reinforced by activating carboxyl groups in a precursor **105** allowing polar bond formation between an electrophilic intermediate **106** and a nucleophile derived from **107** by deprotonation. The unobvious choice of **107** as a precursor for **104** was undoubtedly dictated by its ready availability from purpurogallin **34** by selective oxidative cleavage of the relatively electron rich aryl ring.



Thus, oxidation of **34** with hydrogen peroxide followed by dehydration gave the enol anhydride **107**. It is interesting that Scott utilized purpurogallin (**34**) as a precursor for the C ring of colchicine in contrast to Eschenmosher and Van Tamelen who built the A and B rings of colchicine from **34**.



An A-ring synthon, 3,4,5-trimethoxy acetaldehyde (**106**) was obtained by Arndt-Eistert homologation of 3,4,5-trihydroxybenzoic acid (**108**). Union of the electrophilic A ring synthon **106** with the nucleophilic C-ring synthon **107** was best achieved thermally without base catalysis by a process that starts with an aldol condensation. At 100°C, a lactone **110** was formed, presumably by decarboxylation of an intermediate vinylogous β-keto acid **109**. Further heating of **110** at 190°C gave **112**, presumably by decarboxylation of an intermediate β-keto acid **111**. Reduction and demethylation gave the A+C ring intermediate **104**. The electron rich product **103** from the desired oxidative coupling of **104** was highly susceptible to undesirable further oxidation. Nevertheless, the mild oxidant, $FeCl_3$, in a two phase system gave **103** after paper chromatography in an inert atmosphere albeit in low yield (5%).



It has been suggested that the annelation may involve an ionic process rather than the radical coupling originally envisioned.[5] Thus, utilizing the aryl oxygen functionality at position 2, that was ignored in the polar analysis of **103** above, it can be seen that the bond between the aryl and tropolone rings lies on a consonant circuit between positions 2 and 10. This allows Michael addition of a tropolone nucleophile to an enone electrophile as shown in **113** to deliver **114**. Final adjustment of functionality gave **8** from **103** through **73** as discussed previously.