Preparation and chemical reactivity of 2-chromanols

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Abstract
This review describes the preparation and chemical reactivity of 2-chromanols. These derivatives appear as interesting intermediates in the synthesis of various natural products and biologically active compounds.

Keywords: 2-chromanols, synthesis, chemical reactivity, biological activity

Table of Contents

1. Introduction
2. Preparation of 2-Chromanol Derivatives: General Methods
   2.1 Reduction of dihydrocoumarins by aluminum hydrides
   2.2 Titanocene-catalyzed reduction of dihydrocoumarin
   2.3 Double reduction of coumarins into 2-chromanols
   2.4 Lactols from acetals
   2.5 Intramolecular lactolization
      2.5.1 Hydroformylation of protected 2-hydroxystyrene derivatives
      2.5.2 Palladium-catalyzed conjugate addition
      2.5.3 Asymmetric reactions of β-(2-hydroxyaryl)-α,β-unsaturated ketones and o-hydroxycinnamaldehydes with organoboronic acids
      2.5.4 Asymmetric reactions of (E)-2-(2-nitrovinyl)phenols with carbonyl compounds
3. Reactions of the Cyclic Form of 2-Chromanol Derivatives
   3.1 Deoxygenative reduction
   3.2 Elimination
   3.3 Oxidation
   3.4 Substitution reactions. Formation of acetals
4. Reactions of the Open Form
   4.1 Reactions of the phenol group
   4.2 Addition of carbon nucleophiles
1. Introduction

Substituted chromans, or more precisely chromanol-containing compounds, are a class of benzopyran derivatives frequently found in biologically active natural products such as vitamin E (or tocopherol) or flavanol. Many chromanol and chroman derivatives have been studied and exhibit a variety of activities, including antioxidant\textsuperscript{1,2} or antibacterial\textsuperscript{3,4} properties. The 2-chromanol moiety \textbf{1} appears as an interesting precursor of the above class of compounds and related chromenes but also of various diarylmethanes and sesquiterpenes.

![2-chromanol](image)

This review provides an overview of the synthesis and reactivity of 2-chromanol derivatives. In the first part, we intend to outline the general methods by which the 2-chromanol derivatives are prepared. More detailed preparations will be described in sections 3 and 4. The second and third parts are devoted to the chemical reactivity of the 2-chromanol derivatives. We do not intend to cite all syntheses, but, when appropriate, examples of relevance in medicinal chemistry or natural products will be presented. Unless otherwise noted isolated yields are given.

2. Preparation of 2-Chromanol Derivatives: General Methods

2.1 Reduction of dihydrocoumarins by aluminum hydrides

The most popular preparation of 2-chromanol \textbf{1} is probably the reduction of dihydrocoumarin, which is commercially available. Lactones can be partially reduced to lactols with the participation of a single hydride. Several aluminum hydrides are reported to accomplish such reduction.\textsuperscript{5} We report in Scheme 1 examples of reduction of dihydrocoumarin \textbf{2} to 2-chromanol.
1. Diisobutylaluminum hydride (DIBAL, solution in toluene or hexane) is usually the reagent of choice. It can be used with several solvents (toluene, THF, CH₂Cl₂) but requires low temperature, usually -78 °C, and inert atmosphere. High yields (>80%) are frequently reported.⁶⁻⁸ The reducing power of aluminum hydrides is modified by the introduction of alkoxy groups. In this way, (t-BuO)₃HAlLi in THF is also used with high yields.⁹,¹⁰ The simple addition of one equivalent of absolute ethanol to a sodium bis[2-methoxyethoxy]aluminum hydride solution (SMEAH or Red-Al) leads to a useful reagent for the partial reduction of lactones to lactols.¹¹ Without the above treatment with ethanol the reaction proceeded uncontrolled and gave the lactols only in poor yields. γ-Lactones are reduced selectively at 0 °C but in the case of dihydrocoumarin a lower temperature is required (-60 °C or -70 °C).

Other nucleophiles such as organolithium¹²⁻¹⁴ or organomagnesium¹⁵ compounds add to the carbonyl group of dihydrocoumarins to yield tertiary lactols. The Reformatsky reaction is also described.¹⁶,¹⁷ Applications are provided in sections 3.1 and 3.4.

2.2 Titanocene-catalyzed reduction of dihydrocoumarin
Buchwald et al. have developed a titanocene-catalyzed reduction of lactones to lactols. First, activation of titanocene di-p-chlorophenoxide 3 using PMHS (polymethylhydrosiloxane) and TBAF (tetrabutylammonium fluoride) supported on alumina generates an efficient catalyst for the hydrosilylation of the lactone. A simple aqueous work-up liberates the lactol product.¹⁸,¹⁹ Applied to dihydrocoumarin 2, this process yields 2-chromanol 1 in 87% yield (Scheme 2).
OAr = p-chlorophenoxide

Scheme 2

2.3 Double reduction of coumarins into 2-chromanols

The double reduction of coumarins to 2-chromanols using LiAlH₄ or NaBH₄ has seldom been observed. The double reduction of coumarins by nonracemically ligated copper hydride yields lactols in both good yields and excellent levels of stereoinduction. So, the combination of catalytic amounts of [(R)-DTBM-SEGPHOS]CuH in the presence of stoichiometric DEMS (diethoxymethylsilane) in toluene (or a mixture toluene/THF or dioxane) at room temperature leads to the asymmetric reduction of 4-substituted coumarins 5 (Scheme 3).

Scheme 3

This observation can be rationalized by an initial 1,4-reduction furnishing enolate 7 followed by protonation of the copper-bound enolate with t-BuOH, thus giving dihydrocoumarin 8. Unlike typical saturated alkyl esters and lactones that are stable to CuH, aryl lactones such as 8 are apparently activated toward 1,2-reduction. In this case, lactol 6 is obtained from initially formed...
silyl ether upon workup with TBAF (Scheme 3). Applications of this reduction are given in sections 3.3, 4.3.1 and 4.4.

2.4 Lactols from acetals
Hemiacetals can be prepared by the deprotection of their corresponding acetals. Most methods involve deprotection of acetals under aqueous acidic conditions. Such reactions proceed via an intermediate oxonium ion with the hydroxyl group of the hemiacetal originating from water in the reaction mixture. High yields are generally obtained as illustrated in Scheme 4 with the hydrolysis of acetal 9.

![Scheme 4]

2.5 Intramolecular lactolization
A well-established route for generating the hemiacetal group involves cyclization of hydroxycarbonyl derivatives. When the hydroxyl group is part of the same molecule that contains an aldehyde group, the compound exists almost entirely in the cyclic hemiacetal form. When the aldehyde group is replaced with a ketone, an equilibrium mixture can be obtained, the cyclic form being less favored.

2.5.1 Hydroformylation of protected 2-hydroxystyrene derivatives. Piccolo et al. proposed a preparation of 2-chromanol 1 by hydroformylation of protected 2-hydroxystyrenes such as 11 followed by deprotection of the phenol moiety and spontaneous cyclization of the initially formed 3-(2-hydroxyphenyl)propanal 12 (Scheme 5).
Scheme 5

This route is convenient if the hydroformylation reaction proceeds with high regioselectivity in favor of the linear aldehyde 13 compared to 14. Several experimental conditions (catalyst, temperature, presence of ligand, pressure) were tested in order to form the linear aldehyde 13 in high yields. The best regioselectivity (>99%) was obtained in the hydroformylation catalyzed by the Pt(Xantphos)Cl$_2$ complex in toluene, however, the aldehyde yield was rather low (64%) owing to the unsatisfactory chemoselectivity of the catalytic process. Finally, the deprotection of the phenol moiety of aldehyde 13 to aldehyde 12 followed by spontaneous cyclization afforded 2-chromanol 1 in almost quantitative yield.

2.5.2 Palladium-catalyzed conjugate addition. PdCl$_2$ catalyzes conjugate addition of (2-hydroxyaryl)mercury chlorides 15 with $\alpha,\beta$-unsaturated ketones 16 in a two-phase system.$^{26}$ Intramolecular reactions may follow the conjugate addition and give 2-substituted-2-chromanols. It appears that formation of 2-chromanols is favored when $\text{R}^1$ is other than hydrogen, when $\text{R}^2$ is bonded to the carbonyl group through a sp$^3$ carbon atom and when no strongly electron-withdrawing groups are present on the aromatic ring of the mercurials. Representative examples are given in Scheme 6.
Scheme 6

From the reaction of (2-hydroxyphenyl)mercury chloride with butenone (R₁=R₃=H, R₂=Me), an oil was isolated which was proved to be an equilibrium mixture of the keto form 17 and of the 2-chromanol form 18. The ratio 17/18 was 75/25 in CDCl₃. When R₁ is replaced with a phenyl group, only the 2-chromanol form 19 was obtained. When the aromatic ring was substituted with an electron-withdrawing group, only the keto-phenol 20 was formed (R₁=Ph, R₂=Me, R₃=NO₂).

2.5.3 Asymmetric reactions of β-(2-hydroxyaryl)-α,β-unsaturated ketones and o-hydroxy-cinnamaldehydes with organoboronic acids. Miyaura et al. developed the enantioselective 1,4-addition of arylboronic acids to β-arylenones 21 to give β-diaird ketones 22 in the presence of a dicationic Pd(II) catalyst. 2-Chromanols 23 (cis and trans isomers) are thus obtained as a mixture with 22 (Scheme 7). The yields and enantioselectivities were respectively in a range of 94-99% and 95-99%. The phenyl stabilized keto-phenol form displays a greater stability (22d/23d) and donor groups on the aromatic ring seem to favor the 2-chromanol form (compare 22a/23a with 22c/23c). However, the interpretation of such ratios might be far from straightforward. The Baeyer-Villiger oxidation of 22d-23d to 4-phenyl-2-chromanone shows the formation of the R-product.
Reviews and Accounts

Scheme 7

\[
\begin{align*}
\text{21a } R^1 &= H, R^2 = R^3 = \text{Me} \\
\text{21b } R^1 &= H, R^2 = \text{OMe}, R^3 = \text{Me} \\
\text{21c } R^1 &= R^2 = \text{t-Bu}, R^3 = \text{Me} \\
\text{21d } R^1 &= R^2 = H, R^3 = \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{22a/23a} &= 1/13, 96\% \text{ ee} \\
\text{22b/23b} &= 1/16, 95\% \text{ ee} \\
\text{22c/23c} &= 1/99 \\
\text{22d/23d} &= 2/1, 99\% \text{ ee}
\end{align*}
\]

*enantiomeric excess determined after conversion to 4-aryl-4H-chromene*

\[
\text{catalyst: } [\text{Pd} (S,S\text{-chiraphos})(\text{PhCN})_2] (\text{SbF}_6)_2
\]

Scheme 8

\[
\begin{align*}
\text{24a, 25a } X &= H, R = \text{C}_6\text{H}_5\text{CHCH} \\
\text{24b, 25a } X &= \text{3-MeO}, R = \text{C}_6\text{H}_5\text{CHCH} \\
\text{24c, 25a } X &= \text{5-NO}_2, R = \text{C}_6\text{H}_5\text{CHCH} \\
\text{24a, 25b } X &= H, R = 4\text{-MeO}\text{C}_6\text{H}_5\text{CHCH}
\end{align*}
\]

\[
\begin{align*}
\text{27a } &= 83\%, 92:8 \text{ ee}, 3:1 \text{ dr} \\
\text{27b } &= 93\%, 93:7 \text{ ee}, 4:1 \text{ dr} \\
\text{27c } &= 81\%, 84:16 \text{ ee}, 4:1 \text{ dr} \\
\text{27d } &= 80\%, 93:7 \text{ ee}, 2:1 \text{ dr}
\end{align*}
\]

*enantiomeric ratio determined after oxidation to the corresponding lactone*
The catalytic asymmetric 1,4-addition reactions of organoboronic acids 25 to \( o \)-hydroxycinnamaldehydes 24 have been established using the organocatalyst 26 derived from imidazolidinone. After intramolecular hemiacetalization, 2-chromanols 27 are obtained in high yields and enantioselectivities. Selected examples are given in Scheme 8. The mechanism involves a transient iminium ion 28, the arylvinylboronic acid is activated by the phenol group and able to perform a 1,4-addition to give 29.\(^{29,30}\) The regioselective control of 1,2- versus 1,4-addition in this reaction has also been investigated.\(^{31}\)

### 2.5.4 Asymmetric reactions of \((E)\)-2-(2-nitrovinyl)phenols with carbonyl compounds.

Chiral secondary amines catalyze asymmetric tandem Michael addition-hemiacetalization between aliphatic aldehydes 31 and \((E)\)-2-(2-nitrovinyl)phenols 30 to give 2-chromanols 32. This cascade is initiated by an enamine-mediated Michael addition to the electron-deficient alkene, followed by the intramolecular hemiacetalization. This organocatalytic reaction has been developed by several authors with catalyst, solvent and additive screenings\(^{32-35}\) and extended to propanone\(^{36}\) or \(\beta\)-keto esters.\(^{37}\) High yields and enantiomeric excess are obtained. Selected examples are given in Scheme 9.\(^{35}\)

![Scheme 9](image)

### 3. Reactions of the Cyclic Form of 2-Chromanol Derivatives

2-Chromanol derivatives exist in the form of two isomers: the open chain carbonyl compound and the hemiacetal cyclic form. Because these are rapidly equilibrated, we can divide the reactions of 2-chromanol derivatives in two groups, those occurring on the linear forms and those adopting the cyclic forms.

In sections 3 and 4, alkyl substituted 2-chromanols are available from catalytic hydrogenation of the double bond of the corresponding coumarins followed by reduction of the lactone group (Scheme 10).\(^{8,10,38-40}\) The Pechmann condensation of a phenol and a carboxylic acid or ester containing a \(\beta\)-carbonyl group in the presence of an acid has been widely used for the
preparation of coumarins. For more complex 2-chromanol derivatives the preparation will be described.

Scheme 10

3.1 Deoxygenative reduction
In section 2.2, we described the titanocene-catalyzed reduction of dihydrocoumarin 2. Buchwald et al. combined the room-temperature protocol of lactones reduction with the deoxygenative reduction of lactols. They found that addition of the resin Amberlyst 15 (protonated form) to a solution of the lactol and triethylsilane in CH₂Cl₂ led to the rapid and clean formation of the cyclic ether. From dihydrocoumarin 33 this two-step procedure gives chroman 35 in 67% yield (Scheme 11). The deoxygenative reduction of 2-chromanols using BF₃·Et₂O and PhSiH₃ or Et₃SiH as reducing agents is also described.

Scheme 11

Scheme 12
Colobert et al. reported the addition of the LDA (lithium diisopropylamide) generated lithium anion of (R)-methyl p-tolylsulfoxide (R)-36 to dihydrocoumarin 2. Product 37 was then isolated, in 90% yield, as an equilibrium mixture with cyclic hemiacetal 38. When this mixture was treated sequentially with Et3SiH and TMSOTf (trimethylsilyl trifluoromethanesulfonate) at 0 °C, a stereoselective reductive deoxygenation process took place. Chroman 40 was formed in 86% yield and with an excellent 95:5 diastereoisomeric ratio (Scheme 12).

Scheme 13

The mechanistic pathway proposed in Scheme 12 involves the initial formation of an oxocarbenium ion 39 after ionic cleavage of the C-OH bond by activation with TMSOTf. After coordination of the silane to the sulfinyl oxygen of 39, the attack of the hydride mainly occurred from the lower face (Re-face) of the dihydrobenzopyran unit. This attack occurs in the preferred six-membered chair-like transition state showing the most favorable equatorial situation of the
bulky p-tolyl substituent of the sulfoxide. Starting from this sequence applied to 6-fluoro-2-chromanone 41, the authors proposed a convergent synthesis of the (S,R,R,R)-enantiomer of the antihypertensive drug nebivolol hydrochloride 48 (Scheme 13).

3.2 Elimination

Dehydration of 2-chromanol derivatives provides an access to 4H-chromenes. Dehydration occurs by heating with p-TSA (paratoluenesulfonic acid), oxalic acid, or copper sulfate. Dehydration is also mediated by P₂O₅ in CH₂Cl₂ at 0 °C. Another way entails esterification of 1 or 49 with acetic anhydride followed by pyrolysis of the resulting acetates 50a-b. Further, hydroboration of 4H-chromenes 51a-b yields 3-chromanols 52a-b (Scheme 14). However, 3-chromanols 52a-b are available respectively from direct hydroboration of coumarin (12% yield) and 4,7-dimethylcoumarin (49% yield).

Scheme 14

Dehydration of 2-chromanol derivatives displays various synthetic applications. The 6-methoxy-4H-1-benzopyran-7-ol 53, a major flavour compound of Wisteria sinensis, has been synthesized in 5 steps from 2,4,5-trimethoxybenzaldehyde 54. After selective ether cleavage of 54, subsequent Wittig olefination afforded scopoletin 56. The latter was successively hydrogenated and reduced with DIBAL. The final step was the dehydration of lactol 57 with anhydrous oxalic acid in boiling benzene (Scheme 15).

Scheme 15
2-Chromanols obtained as described in sections 2-5-3 and 2-5-4 are easily dehydrated to 4H-chromenes using \( p \)-TSA as catalyst in refluxing toluene. Starting from 32a and 23a-d, 4H-chromenes 58 and 59a-d are respectively formed in high yields (Scheme 16).\(^{28,35}\) 4-Aryl-4H-chromenes are identified as potent apoptosis inducers.\(^{51,52}\) Hydrogenation of the nitro group of 58 and protection of the amino group afforded chromene 60 or chroman 61 according to the reduction time. Compounds 60 and 61 are drug-like molecules; such structures possess potent anti-ischemic properties and are important as anti-hypertensives, blood vessel spasmolytics and potassium channel blockers.\(^{35}\)

![Scheme 16](image)

### Scheme 16

#### 3.3 Oxidation

Several 2-chromanone derivatives are prepared from the corresponding 2-chromanols using \( \text{KMnO}_4 \), PCC (pyridinium chlorochromate) or Jones oxidation in high yields.\(^{23,24,29,33-35,53-55}\) Moorthy \textit{et al.} have prepared a series of dihydroisocoumarins by oxidation of the corresponding lactol using IBX (\( o \)-iodoxybenzoic acid) in an \( \text{EtOAc-DMSO} \) (9:1) mixture at reflux. With 6-methyl-2-chromanol 62, a non benzylic hemiacetal, the best yields were obtained using benzene or chloroform (Scheme 17).\(^{35,56}\)
Scheme 17

We have mentioned in section 2.3 the double reduction of coumarins by nonracemically ligated copper hydride. An application leading to GPR40 agonist 64 is displayed in Scheme 18. The coumarin derivative 65 was prepared in 2 steps from 4-hydroxycoumarin 66 using a Suzuki coupling on the corresponding tosylate. Asymmetric reduction of 65 with catalytic [(R)-DTBM-SEGPHOS]CuH was followed by a PCC oxidation of the resulting lactol 67. Lactone 68 was obtained in 86% yield from 65 and 97% ee. Saponification (LiOH) of 68 is known to produce 64 in an enantiopure form. Such strategy involving asymmetric conjugate reduction followed by oxidation was also proposed for the formal synthesis of (+)-heliannuol A, SB-217242 and SB-209670.

Scheme 18

3.4 Substitution reactions. Formation of acetals
The substitution reactions of the hydroxyl group are summarized in Scheme 19. 2-Chromanol 1 is chlorinated by SOCl₂ in the presence of ZnCl₂ in 80% yield. 2-Chromanols are converted to...
acetals when treated with an alcohol in acidic medium.\textsuperscript{26,35,36,59} So 19 was converted into the 2-ethoxychroman derivative 70 through an acid-catalyzed ethanolysis in 98\% yield.\textsuperscript{26} Sometimes, a different sequence, in which lactol is first treated with SOCl\textsubscript{2} and then the alcohol is required.\textsuperscript{6} Using DAST, (diethylaminosulfur trifluoride) the α-fluoroether 71 is obtained in 81\% yield.\textsuperscript{60,61} The hemiacetal function of 2-chromanol derivative 49 reacts with benzeneselenol to give the α-phenylselenyl ether 72 but is also partially reduced to the chroman derivative. This drawback was overcome using the corresponding acetate 73.\textsuperscript{62} α-Phenylselenyl ethers provide an access to enol ethers and chemistry of α-alkoxy anions.

![Scheme 19](image)

The (2\textit{R}, 4′\textit{R}, 8′\textit{R})-α-tocopherol (vitamin E) is a prototypal antioxidant. Cohen \textit{et al.} described the synthesis of (2RS, 4′\textit{R}, 8′\textit{R})-α-tocopherol as the corresponding benzyl ether 74 (Scheme 20). This form of vitamin E is also called 2-ambo-α-tocopherol and is a 1-1 mixture of epimers.\textsuperscript{63} The acetal 75, derived from the reaction of methylvinylketone 76 with trimethylhydroquinone 77, was first treated with benzyl chloride. The acetal group was then hydrolyzed giving 2-chromanol 78 which appears as a key intermediate in preparations of vitamin E or analogues (see section 4-1).\textsuperscript{64-66} The yields displayed in Scheme 20 for the
preparation of 78 are from reference 66. Treatment of the hemiacetal 78 with HCl in ether at 0 °C afforded chloride 79 in 93% yield. The substitution reaction of 79 with the C16-side chain Grignard reagent 80 was studied in some detail to prevent elimination (formation of the chromene derivative). The desired reaction was favored in diethyl ether (compared to THF) and at low temperature but a moderate yield was obtained. The authors proposed the intermediacy of an oxonium ion in these substitution reactions.6

Scheme 20

Colobert et al. described an enantioselective total synthesis of the natural γ-tocopherol metabolite (S)-γ-CEHC 81 (Scheme 21). The initial Friedel-Crafts alkylation of 2,3-dimethylhydroquinone 82 was followed by the protection of the phenol group with TBSOTf (tert-butyldimethylsilyl trifluoromethanesulfonate). Then the Li anion of (S)-methyl p-tolyl sulfoxide (S)-36 adds to the carbonyl group of the protected lactone 83. After acetalization of lactol 84 in 85% yield, the resulting 2-methoxy-3,4-dihydropyran 85 was submitted to the sulfoxide-directed TiCl₄-promoted nucleophilic alkylation using allyl trimethyl silane. The major stereoisomer 86 was obtained in 67% yield and results from the attack to the upper face of the oxocarbenium intermediate 87. (S)-γ-CEHC 81 was obtained in 5 steps from 86 and 18% overall yield starting from 82.13 A similar sequence was used during the total synthesis of (2R, 4′RS, 8′RS)-α-tocopherol.67
4. Reactions of the Open Form

4.1 Reactions of the phenol group

The hydroxyl group in phenols undergoes several reactions of alcohols such as ether synthesis and esterification. The phenol group of the open form of 2-chromanol derivatives, after conversion to the phenoxide ion, is methylated using dimethylsulfate or methyl iodide.\textsuperscript{27,36} Esterification of the phenol group was used for the synthesis of chiral chromans.\textsuperscript{40,68} The synthesis of chiral chromans via Pd-catalyzed imolecular asymmetric allylic alkylation (named AAA) of phenol allyl carbonates has been extensively studied.\textsuperscript{69,70,40} Trost’s group explored in detail this reaction and obtained high yields and enantioselectivities under the conditions described in Scheme 22. First, acetal 88 was prepared by the reaction of phenol 89 with methylvinylketone 76 (see section 3.4). The resulting acetal 88 was hydrolyzed with diluted HCl to give 2-chromanol derivative 90. The phenol group of the open form of 90 was then protected by reaction with acetyl chloride in 98% yield. Steric hindrance of the tertiary hydroxyl group of 90 seems here to favor acetylation of the phenol group.\textsuperscript{71} After a Wittig reaction, both ester groups of 92 were reduced to yield phenol 93. Esterification of 93 to the desired carbonate 94 was then followed by the AAA reaction to yield the chiral chroman 95.\textsuperscript{40}
Tietze et al. described an enantioselective palladium-catalyzed total synthesis of vitamin E employing a domino Wacker-Heck reaction.\textsuperscript{66} The phenol group of 2-chromanol 78 (see section 3-4) was esterified in 94% yield by using acetic anhydride dissolved in pyridine. Formation of the double bond using the Lombardo reagent followed by saponification afforded the desired substrate 97. The Wacker-Heck reaction of 97 and methylvinylketone 76 afforded the intermediate 98 in 84% yield and 97% ee. Vitamin E 99 was obtained in 6 steps from 98 as a 1:1 mixture together with the (4′S)-epimer (Scheme 23).
Scheme 23

4.2 Addition of carbon nucleophiles
4.2.1 Organometallics. Transition metal catalyst. Grignard and alkyllithium reagents add to the carbonyl group to produce alcohols. The nucleophilic addition of the carbanion formed from 2-picoline to the open form of 2-chromanol 1 leads to a pyridine derivative.\(^\text{72}\)

Xenognosin 100, the first identified host recognition substance for parasitic angiosperms, has been synthesized in seven steps from 7-hydroxycoumarin 101. 2-Chromanol derivative 102 was obtained in an usual way after hydrogenation of the double bond, protection of the phenol group and DIBAL reduction. The complete carbon skeleton was accessible in 85% yield through the reaction of 102 with the Grignard reagent formed from the TBDMS (tert-butyldimethylsilyl) protected \(p\)-bromophenol. Xenognosin 100 was then obtained in 3 steps (Scheme 24).\(^\text{73}\)

Scheme 24

A catalytic system of \([\text{Ni(acac)}_2]/\text{diene/Et}_3\text{B}\) (acac=acetylacetonato) promotes homoallylation of aldehydes and cyclic hemiacetals.\(^\text{74,75}\) Applied to 2,3-dimethylbutadiene 104 and 2-chromanol 1, phenol 105 was obtained in good yield (Scheme 25). The stereoselectivity was excellent, the reaction providing only the 1,3-\textit{anti} isomer.
4.2.2 Wittig reaction. The Wittig reaction of 2-chromanol 1 with isopropyltriphenylphosphonium bromide in the presence of KHMDS (potassium hexamethyldisilazane) gives phenol 106a in 69% yield. With ethyl 2-(triphenylphosphoranylidene)propanoate, the E isomer 106b was obtained in 92% yield (Scheme 26).

Scheme 26

The preparation of isotwistane derivatives is challenging since a few naturally occurring sesquiterpenes have the unique isotwistane framework. The Wittig reaction of 2-chromanol 1 with ethyl 2-(triphenylphosphoranylidene)acetate in benzene yields ester 107a. The E isomer was the major product. Isotwistane derivative 108a was obtained in 26% overall yield from 1 (Scheme 27). Even if this yield appears modest the brevity of the sequence makes this method convenient. This preparation was generalized to alkyl substituted 2-chromanols. Particularly 7-ethyl-2-chromanol 109 was the precursor of coronafacic acid 110, the acidic component of coronatine, an amide which induces lesions on the leaves of Italian rye grass and hypertrophic growth of potato tuber tissue.
Pettus et al. prepared (-)-curcuphenol 111 as an intermediate in the preparation of \(\alpha\)-cedrene 112, \(\alpha\)-pipitzol 113 and \(\text{sec}\)-cedrenol 114, three members of the cedranoid family (Scheme 28).\(^{78}\) \(\alpha\)-Cedrene is an approved food preservative while \(\text{sec}\)-cedrenol has been shown to be a potent stimulant of the histamine H3 receptor. The latter might prove useful for the prevention and treatment of bronchial asthma, hyperlipidemia and inflammation. The enantioselective procedure begins by the addition of 2 equiv of MeMgBr to a flask containing the salicylaldehyde 115 and the enol ether (+)-116 (3 equiv). The resulting dianion undergoes mono carboxylation with Boc\(_2\)O (di-tert-butyl dicarbonate) leading to the generation of \(\text{o-QM}\) 118 (o-quinone methide).\(^{79}\) Then a diastereoselective Diels-Alder reaction proceeds to afford the chroman ketal 119. Hydrolysis of 119 catalyzed with CSA (camphorsulfonic acid) afforded lactol 120. A Wittig reaction using ClPh\(_3\)PCH\(_2\)OCH\(_3\) in the presence of \(n\)-BuLi in THF afforded, after hydrolysis of the enol ether group, aldehyde 121 in 84% yield. Another Wittig reaction gave (-)-curcuphenol 111.\(^{80}\)

\[
\begin{align*}
\text{HO} & \quad \text{MeMgBr} \\
\text{H} & \quad \text{Et}_2\text{O}, 0 \, ^\circ\text{C} \\
\text{O} & \quad \text{then Boc}_2\text{O} \\
\text{Ph} & \quad -40 \, ^\circ\text{C} \\
\text{115} & \quad \text{BocO} \\
\text{O} & \quad \text{BrMgO} \\
\text{117} & \quad \text{o-QM 118} \\
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{119 (73%, 16:1 dr)}
\end{align*}
\]

\[
\begin{align*}
\text{CSA} & \quad \text{CH}_3\text{CN, H}_2\text{O, reflux} \\
\text{115} & \quad \text{HO} \\
\text{O} & \quad \text{120 (92%)} \\
\text{1} & \quad \text{CIPh}_3\text{PCH}_2\text{OCH}_3 \quad (2.5 \, \text{equiv}) \\
\text{1} & \quad \text{n-BuLi (2.3 \, \text{equiv}), THF} \\
\text{1} & \quad \text{aq HCl} \\
\text{1} & \quad \text{121 (84%)} \\
\text{HO} & \quad \text{IPh}_3\text{PCH(CH}_3\text{)}_2 \quad (2.5 \, \text{equiv}) \\
\text{CHO} & \quad \text{n-BuLi (2.4 \, \text{equiv}), THF} \\
\text{1} & \quad \text{3 steps} \\
\text{1} & \quad \text{\(\alpha\)-cedrene 112 (13% overall yield from 115)} \\
\text{1} & \quad \text{4 steps} \\
\text{1} & \quad \text{\(\alpha\)-pipitzol 113 (14% overall yield from 115)} \\
\text{1} & \quad \text{4 steps} \\
\text{1} & \quad \text{\(\text{sec}\)-cedrenol 114 (9% overall yield from 115)}
\end{align*}
\]

Scheme 28

The Wittig reaction of 2-chromanols affords intermediates in the preparation of chiral chromans.\(^{35,36}\) The esters 107a and 122 prepared from the Wittig reaction of 2-chromanols 1 and 62 are precursors in 4 steps of carbonates 123a-b (Scheme 29). Chiral chromans 124a-b were
prepared in good yields and enantioselectivities from the asymmetric allylic alkylation of carbonates 123a-b as described in section 4.1.40,69,70

Scheme 29

Amino substituted 2-(chroman-2-yl) acetic acid esters are intermediates for producing platelet aggregation inhibitors and/or are themselves potent therapeutic agents.81 Indeed coupling of the amino group with benzoyl derivatives constitutes an additioonal step towards therapeutic agents.82 2-Chromanol 1 appears as a precursor of amino-substituted chromans. When a Wittig reaction is performed in the presence of a base, an oxa-Michael addition follows leading to the formation of a chroman derivative. Thus, condensation of 2-chromanol 1 with ethyl 2-(triphenylphosphoranylidene) acetate followed by the addition of EtONa gives acetate 125 in 89% overall yield (from dihydrocoumarin, the precursor of 2-chromanol 1). Then amino substituted 2-(chroman-2-yl)acetate 126 was obtained in 3 steps (Scheme 30). Resolving chiral intermediates to provide the desired enantiomers complete this work.81

Scheme 30
Such amino-substituted chromans can also be formed via a Wittig-oxa-Michael step realized on 2-chromanols substituted at position 6 by a protected amino group or a nitro group.\textsuperscript{83-86} The drawback of these approaches is the need to perform an optical resolution during the synthesis. In this field, Merschaert \textit{et al.} proposed a new asymmetric synthesis of 2-substituted chiral chromans using a chiral base in the Wittig-oxa-Michael step.\textsuperscript{87}

The Wittig-oxa-Michael reaction on chromanol derivative 127 was used as a step for the synthesis of \((2R, 4'R, 8'R)-\alpha\)-tocopherol 99 (vitamin E). The Wittig-Horner reaction performed at room temperature with trimethyl phosphonoacetate was followed by heating at reflux in THF (Scheme 31) to yield the cyclization product 128.\textsuperscript{64}

\[
\begin{align*}
\text{HO} & \quad | \quad \text{O} \\
\text{114} & \quad | \quad \text{O} \\
1) \text{acetic anhydride} & \quad \text{AcO} \\
2) \text{aq HCl, acetone reflux} & \quad \text{OH} \\
\text{127 (90\% from 77, the precursor of 75, see scheme 20)} & \quad \text{trimethyl phosphonoacetate} \\
\end{align*}
\]

\[
\begin{align*}
\text{AcO} & \quad | \quad \text{CO}_2\text{Me} \\
\text{128} & \quad | \quad \text{HO} \\
\text{saponification} & \quad \text{HO} \\
\text{129 (80\% from 127)} & \quad \text{CO}_2\text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad | \quad \text{P} \\
\text{O} & \quad \text{O} \\
\text{MeO} & \quad | \quad \text{MeO} \\
\end{align*}
\]

\[
\begin{align*}
\text{NaH, THF, 23 \text{ \degree C, 18 h}} & \quad \text{then reflux, 4 h} \\
\end{align*}
\]

\[128\]

\[\text{129 (80\% from 127)}\]

\[\text{vitamin E 99}\]

\[\text{Scheme 31}\]

4.2.3 Knoevenagel condensation. In an approach to the synthesis of trichothecene, Goldsmith \textit{et al.} condensed 4,7-dimethylchromanol 49 with diethyl malonate in the presence of piperidine. Thus a tandem Knoevenagel-Michael addition takes place and the diester 130 is formed in 75\% yield (Scheme 32).\textsuperscript{39} Cheng \textit{et al.} described the preparation of compounds that modulate PPAR activity. The thiazole derivative 131 provides an example (Scheme 32). The Knoevenagel condensation of 2-chromanol 1 with dimethyl malonate afforded dimethylester 132 in 47\% yield. Compound 131 was prepared in 4 steps from 132, nevertheless only poor yields were obtained.\textsuperscript{88}
Reviews and Accounts

Scheme 32

4.3 Addition of amines
4.3.1 Reductive amination. The amino group adds to 2-chromanol derivatives. 2-Chromanol 1 condenses with mercaptoethylamine derivatives to form thiazolidine rings. A wide variety of aldehydes, ketones and lactols undergo reducto amination when added to react with 3-pyrrolines in the presence of PhCO$_2$H as catalyst. This reaction utilizes the inherent reducing power of 3-pyrroline to perform the equivalent of a reductive amination and form N-alkylpyrroles. Treatment of five- and six-membered lactols produces hydroxy pyrroles while reducto amination of 2-chromanols 1, 133, 134 affords pyrrolyl phenols 135a-c in good yields (Scheme 33).

Pyrrole derivatives have great importance in organic chemistry because they are present in many natural and medicinal products, and they are also very convenient precursors for biologically important compounds.

Scheme 33

The reductive amination of 4-phenyl-2-chromanol derivatives appears as a step in the preparation of several therapeutic products. 4-Phenyl-2-chromanol 136 was prepared in two steps from o-benzylphenol 137. Initially a dilithium species was formed and, quenching with allyl bromide, gave the racemic allyl compound 138. This was subjected to ozonolytic cleavage to
give, after cyclization, 136. The reaction of 4-phenyl-2-chromanol 136 (mixture of diastereoisomers) with S-phenylethylamine in the presence of NaCNBH₃ gave a 1:1 mixture of 2′-hydroxy derivatives of fendiline 139a and 139b in 33% yield (Scheme 34).⁹³,⁹⁴

\[
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{Ph} \quad \text{Ph} \\
\text{Ph} \quad \text{Ph} \\
\text{Ph} \quad \text{Ph}
\end{array}
\]

Scheme 34

Both diastereoisomers, which were cleanly isolated by column chromatography, appear as potent relaxers of isolated arteries. Such fendiline analogues also display ability to inhibit growth of human leukemia cells.

Lennon et al. prepared a set of quaternary ammonium compounds which are useful medicaments for treatment of asthma, breathing or urinary disorders, allergic rhinitis and rhinorrhea due to the cold. For this work, they used the reductive amination of 4-phenyl-2-chromanol derivatives followed by quaternization of the tertiary amino group.⁹⁵

The (S)-tolterodine (S)-140, which provides spasmolytic activity against urinary disorders and intestinal spasms, is available after reductive amination of (S)-6-methyl-4-phenyl-2-chromanol 141.⁹⁶ The coumarin derivative 142 is formed by a Heck reaction between 2-bromo-4-methylphenol 143 and methyl trans-cinnamate 144. Asymmetric hydrogenation of coumarin 142 using [Rh(COD)Cl]₂ (COD = 1,5-cyclooctadiene) and S,S-Chiraphos as chiral ligand in a stainless steel autoclave under a H₂ pressure gives the hydrogenated adduct 145 (84% yield, S/R = 90/10). The open product 146 is formed together with 145 but cyclizes by standing or refluxing in toluene with catalytic amount of p-TSA. The hydrogenated lactone 145 was reduced to lactol 141 with DIBAL. The crude lactol 141 was then submitted to reductive amination conditions (Scheme 35).
The (R)-tolterodine (R)-140, a potent and competitive muscarinic receptor antagonist drug used to treat urinary incontinence and other bladder disorders, is also available from coumarin 142 alternatively prepared from a Wittig reaction. First, asymmetric conjugate addition of nonracemically ligated CuH (see section 2.3) on coumarin 142 yields 149. The reaction of 149 with diisopropylamine under reductive amination conditions afforded (R)-140 in 93% yield (Scheme 36).[^23][^97]
4.3.2 Domino reaction. The tetrahydroquinoline moiety is an important structural feature of various natural products and pharmaceutical agents that have exhibited a broad range of biological activities. The $\text{InCl}_3$-catalyzed reaction of aromatic amines with cyclic hemiacetals in water yields tetrahydroquinoline derivatives. The sequence presumably proceeds through N-arylimine formation followed by a hetero Diels-Alder reaction. So the reaction of 2-chromanol 1 and aniline produced [2-$(o$-hydroxyphenyl)]ethyl substituted tetrahydroquinolines 150a-b in 49% yield (Scheme 37).

Scheme 37

4.4 Hydride reduction

The hydride reduction of the lactol group of a 2-chromanol leads to a primary alcohol. This reduction was applied to one of the synthetic steps towards $(R$)-4-methoxydalbergione 151. The latter belongs to a family of optically active quinones (dalbergiones) found in tropical woods. These natural products are known to be responsible for inducing allergic contact dermatitis. The coumarin derivative 152 was first prepared from a Wittig reaction between 2-hydroxy-4-methoxybenzophenone 153 and ethyl 2-(triphenylphosphoranylidene)acetate. The asymmetric conjugate reduction of coumarin 152 (see section 2.3) yields chiral 2-chromanol derivative 154.

The crude lactol 154 was then reduced with LiAlH$_4$ to give diol 155 with an excellent yield (97%, 2 steps) and enantiomeric excess (99% ee). After the selective alkylation of the phenolic hydroxyl group of 155, $(R$)-4-methoxydalbergione 151 can be obtained in 4 steps as described in literature (Scheme 38).

Pettus et al. completed a synthesis of $(+)$-R-mimosifoliol 156, a natural product isolated from the rootwood of Aeschynomene mimosifolia Vatke (Leguminosae). The preparation involves 9 steps from benzaldehyde derivative 157 with a 35% overall yield. First, 157 was bis-protected in 2 steps resulting in 158. When 158 was subjected to PhMgBr in the presence of enol ether $(--)$-116, the adduct 159 was formed. This step is an enantioselective cycloaddition of the generated o-quinone methide $(o$-QM 160) with the chiral enol ether $(--)$-116 (see section 4-2-2). The $(o$-QM results from a series of events (cascade), the first step being the nucleophilic addition of PhMgBr to the aldehyde group of 158. Hydrolysis of 159 catalyzed with CSA afforded 2-chromanol derivative 161. The LiAlH$_4$ reduction of lactol 161 afforded 162 in 82% yield. $(+)$-Mimosifoliol 156 was then obtained in 4 steps from 162 (Scheme 39).
Scheme 38

Scheme 39
5. Conclusions

This review focuses on the 2-chromanol moiety. Chromanol derivatives are interesting intermediates to obtain compounds with biological properties.

First of all, we described methods of preparation of 2-chromanol derivatives. If the reductions of dihydrocoumarins or coumarins have been efficiently developed, they can suffer from difficult conditions. However, deprotection of cyclic acetal can lead easily to the expected hemiacetal while intramolecular lactolization of the corresponding hydroxycarbonyl derivatives allows the use of a larger variety of substrates.

Then, reactivity of 2-chromanol derivatives has been studied. They can react on the cyclic or on the open form to yield more complex structures. Moreover, some asymmetric synthesis have been developed in order to obtain natural products or biologically active compounds with good to excellent enantiomeric excess.

6. References


Authors’ Biographies

JM Mattalia received his PhD in 1992 at the Faculty of Saint-Jérôme in Marseille under the supervision of Professor Michel Chanon. After postdoctoral studies in the group of Prof. CJM Stirling at the University of Sheffield, he joined the Aix-Marseille University as assistant professor. His main research interests are in the field of mechanism studies and heterocyclic chemistry.
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