SYNTHETIC STRATEGIES FOR THE SYNTHESIS OF BENZO[*c*]CHROMENE SCAFFOLD

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Dedicated to the memory of Dr. Calogero Antonio Caccamisi

Abstract. *Molecules with a benzo[c]chromene heterocyclic ring system are present in nature and have shown a wide range of pharmacological activities. The interest in this heterocyclic core has encouraged the development of strategies for its synthesis by both organic and pharmaceutical chemists. In this chapter, the synthetic strategies for the preparation of the benzo[c]chromene scaffold will be discussed.*

Contents

1.Introduction

The 6*H*-benzo[*c*]chromene is a heterocyclic structure recurrent in numerous organic compounds of natural origin, which have proved to be of significant pharmacological interest. For example, this heterotricyclic structure constitutes the backbone of the phytocannabinoid class[1] (Figure 1), among which we mention two compounds isolated from the *Cannabis sativa* plant, Cannabinol **I** (CBN) and the related Cannabinolic Acid **II** (CBNA). CBN interacts with G-protein-coupled CB1 and CB2 receptors and, unlike Δ^9-THC, it does not show psychotropic effects, but it displays antibacterial activity.[2] Moreover, it possesses antioxidant properties comparable to vitamin E, due to the ability to scavenge free radicals and to protect from oxidation processes.[3] CBNA is a non-psychoactive cannabinoid and its monoterpenol ester showed moderate antimicrobial activity against *C. albicans* and mild antimalarial activity against *P. falciparum*.[4]

Recently, other compounds containing the nucleus of the 6,6-dimethyl-6*H*-benzo[*c*]chromene, Pulchrol **III** and Pulchral **IV** (Figure 1), have been identified as secondary metabolites of the *Bourreria pulchra* plant, traditionally used in the Yucatan peninsula for antiviral and antipyretic preparations as well as to treat skin diseases.[5] Compound **III** has been shown to possess in vitro antiprotozoal activity against *Leishmaniamexicana* and *Trypanosomacruzi*, while both compounds **III** and **IV** are moderately active against *Leishmaniabraziliensis*.[6]

Other compounds sharing the benzo[*c*]chromene skeleton have been discovered by studying small marine invertebrates which feed themselves by filtering the waters on the seabed. A varied number of meroterpenes with a benzochromene structure have been identified, some of which are distinguished by their potential therapeutic activity. In particular, Didehydroconicol **V** was isolated from the marine invertebrate *Aplidium aff. Densum* (Figure 2). This compound showed antiproliferative activity on *Escherichia coli* and *Micrococcus luteus* bacteria.[7]

Three new prenylated phenols with benzo[*c*]chromene skeleton, namely Ganocochlearin C **VI**, Ganocochlearin D **VII**, and Cochlearol T **VIII**, were recently isolated from the fruiting bodies of *Ganoderma cochlear*, a mushroom widely used in traditional Chinese medicine (Figure 2).[8] Initial biological evaluations revealed that these natural products exhibit various potential activities, such as antioxidant, neuroprotective, and renoprotective properties.[9]

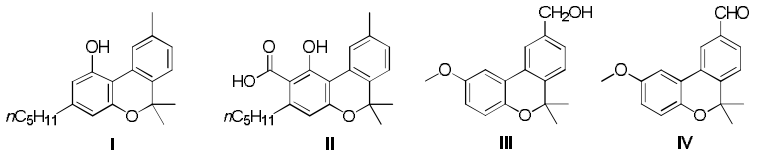


Figure 1. Notable natural compounds with the benzo[*c*]chromene scaffold: Cannabinol **I**, Cannabinolic Acid **II**, Pulchrol **III** and Pulchral **IV**.

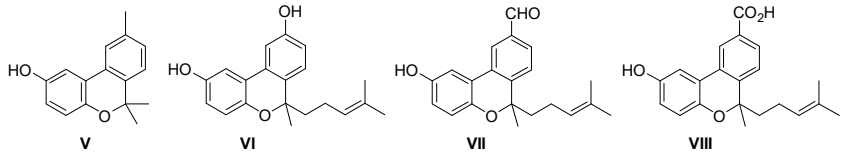


Figure 2. Meroterpenoid natural compounds having a benzo[c]chromene core: Didehydroconicol **V**, Ganocochlearin C **VI**, Ganocochlearin D **VII**, and Cochlearol T **VIII**.

Because of their interesting bioactivity, these groups of natural products have served as important sources for the development of new drug candidates based on the benzo[*c*]chromene scaffold, aimed at providing new bioactive and selective molecules. Indeed, compound **IX** (Figure 3) is a partial, selective and high-affinity agonist for the CB1 receptor,[10] therefore it is intended as a useful tool in the study of cannabinoid receptors. Compound **X** (also known as 11-hydroxy Cannabinol) is also a powerful CB1 agonist, endowed with a much higher affinity for the receptor than Cannabinol **I**.[11] A completely different pharmacological activity is typical of compound **XI**, which opens up a possible development of a new class of non-steroidal selective modulators of progesterone receptors (SPRMs).[12]

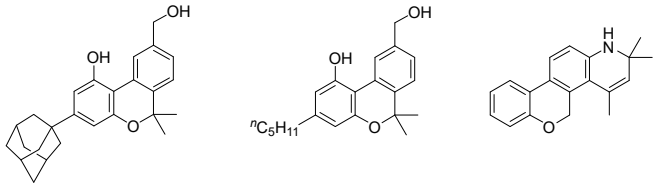


Figure 3. Synthetic biologically relevant compounds showing the benzo[*c*]chromene core.

In addition, material science benefits from the peculiar properties of the benzo[*c*]chromene core conferring semiconducting properties in charge-transfer materials, as reported for the two low-bandgap polymers PBCDTBT and PBCDPP2T (Figure 4).[13]

The interest in this heterocyclic core has encouraged the development of strategies for its synthesis by both organic and pharmaceutical chemists. This chapter presents the strategies developed in the recent years for the preparation of the 6*H*-benzo[*c*]chromene scaffold.

2. Synthetic strategies for 6*H*-benzo[*c*]chromenes

In view of the structural features of 6*H*-benzo[*c*]chromene, five main different approaches for its formation can be identified, *i.e.,* from appropriately functionalized biaryls in which the annulations to a

pyran ring can be obtained through the formation of a new C–C or C–O bond (Scheme 1, path A). On the other hand, the Csp^2–Csp^2 bond formation from substituted aryl benzyl ethers provides a second practical route for the construction of this scaffold (Scheme 1, path B). The base-catalysed annulations to form a new benzene ring starting from chroman-4-one has been also explored (Scheme 1, path C). The intramolecular Diels-Alder approach *via* a cascade pathway differs from previous synthetic methods because results in the simultaneous formation of the pyran moiety and one of the two aromatic rings of the 6*H*-benzo[*c*]chromene (Scheme 1, path D). Finally, functionalized 6*H*-benzo[c]chromenes were recently obtained from 3-alkenyl chromenes by intermolecular Diels-Alder/aromatization sequence (Scheme 1, path E).

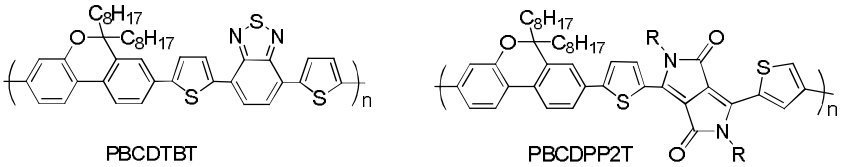
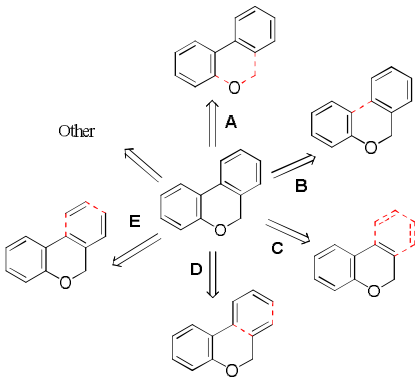


Figure 4. Incorporation of the benzo[*c*]chromene moiety in conducting polymers for material science and organic photovoltaic applications.



Scheme 1. General overview of the synthetic approaches to the synthesis of the benzo[*c*]chromene core.

3. Synthesis of the biaryl system and subsequent cyclization to chromene

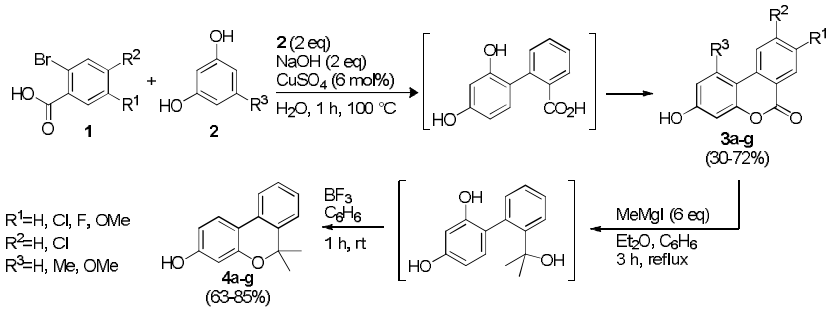
3.1. Synthesis *via* a chromanone intermediate

Since 1974, biaryl lactones have been widely used as intermediates in the preparation of benzo[*c*]chromenes. In fact, Devlin[14] described the synthesis of 6*H*-6,6-dimethyl-benzo[*c*]chromenes starting from benzo[*c*]chromen-6-ones **3** (Scheme 2) which were obtained through a process developed in 1929 by Hurtley. This process consisted in a one-pot multistep copper-catalysed reaction of substituted 2-bromobenzoic acids **1** with 2-substituted resorcinols **2**, in which the formation of the biaryl system is followed by the lactonization of the intermediate biaryl acids. The treatment of these lactones **3** with an excess of methyl magnesium iodide and the dehydration-cyclization of the carbinol intermediates by boron trifluoride gave the substituted benzo[*c*]chromenes **4a-g** in good yields.

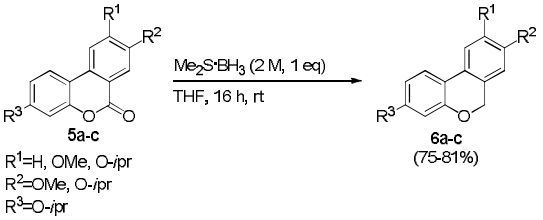
Hajela and co-workers prepared some benzo[*c*]chromen-6-ones **5a-c** with a similar approach.[15] The successive reduction with borane-dimethyl sulfide complex at room temperature furnished the corresponding 6*H*-benzo[*c*]chromenes **6a-c** in excellent yields (Scheme 3).

A very similar approach was employed by Sun *et al.* in the preparation of a series of estrogen β-receptor agonists.[16] Unfortunately, no yields and experimental data were reported by the authors. As shown in Scheme 4, the authors prepared some 6,6-unsubstituted-6*H*-benzo[*c*]chromenes **8** (R^3,R^4=H) and 6-monosubstituted-6*H*-benzo[*c*]chromenes **8** (R^3=H, R^4=Me, Et, *n*-Pr, *i*-Bu) by classical reduction of

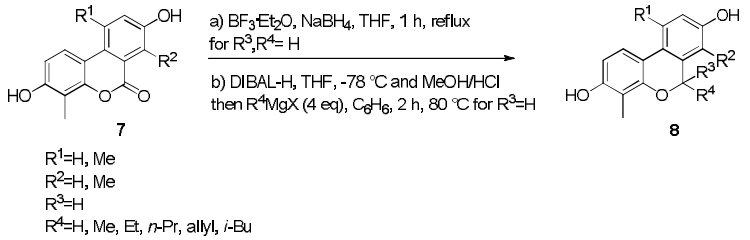
6*H*-benzo[*c*]chromene-6-one **7** with boron trifluoride etherate-sodium borohydride or by reducing the lactone **7** to lactol with DIBAL-H in THF and then reacted with various Grignard reagents in benzene.



Scheme 2. Three-steps preparation of 6*H*-6,6-dimethyl-benzo[*c*]chromenes from 2-bromobenzoic acids and resorcinols.



Scheme 3. Borane-dimethylsulfide complex reduction of 6*H*-benzo[*c*]chromen-6-ones to the corresponding 6-unsubstituted-6*H*-benzo[*c*]chromenes.

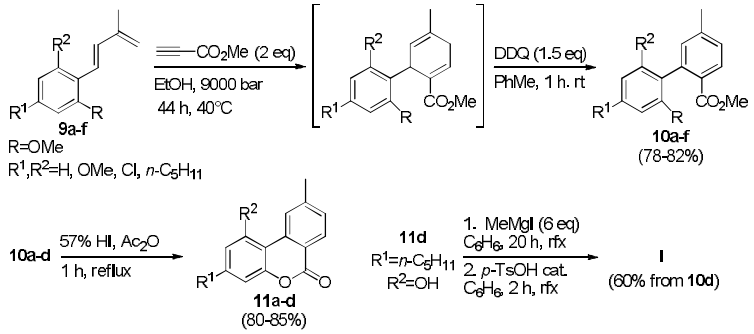


Scheme 4. Reductive approach to the synthesis of the 6-alkyl-substituted 6*H*-benzo[*c*]chromenes starting from the corresponding 6*H*-benzo[*c*]chromen-6-ones.

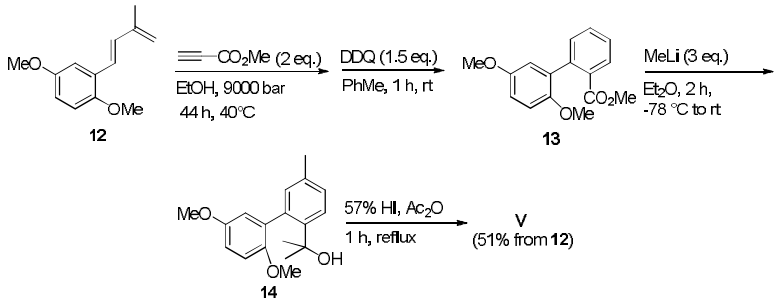
Minuti and co-workers used a Diels-Alder reaction of 1-(alkoxy/alkyl-phenyl)buta-1,3-dienes **9a-f** with methyl propiolate as dienophile under 9 kbar pressure for the metal-free preparation of differently substituted biaryl esters **10a-f** (80-85%) after DDQ oxidation of the cyclohexadienylbenzene cycloadduct intermediates (Scheme 5).[17] Then, biaryl esters could be employed for the preparation of benzo[*c*]chromene-6-ones **11a-d** , possible precursors for the synthesis of 6*H*-benzo[*c*]chromenes. Thus, the authors reported a simple synthesis of Cannabinol **I** by demethylative lactonization of biaryl ester **10d** with hydrogen iodide in acetic anhydride to give the corresponding 6*H*-benzo[*c*]cromene-6-ones **11d** in 81% excellent yield (Scheme 5). Finally, Cannabinol **I** was obtained in 75% good yield from chromenone **11d** through methylation with an excess of methylmagnesium iodide and the subsequent treatment of the crude product with catalytic *p*-TsOH.

In a similar way, the same authors reported in 2015 a high-yielding synthesis of Didehydroconicol **V** in four steps and 51% overall yield starting from the alkoxy-substituted (phenyl)buta-1,3-diene **12** (Scheme

6).[18] Notably, the biaryl ester **13** was treated with an excess of MeLi at –78 °C to furnish the carbinol intermediate **14**. This was followed by a cyclization reaction with a mixture of acetic anhydride and 57% aqueous hydrogen iodide at reflux for 1 hour to give the desired Didehydroconicol **V**.



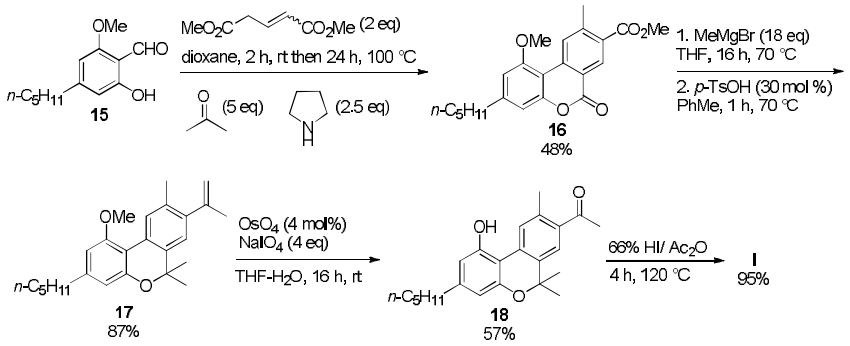
Scheme 5. Synthesis of 6*H*-benzo[*c*]chromen-6-ones **11a-d** through a hyperbaric intermolecular Diels-Alder reaction and total synthesis of Cannabinol **I**.



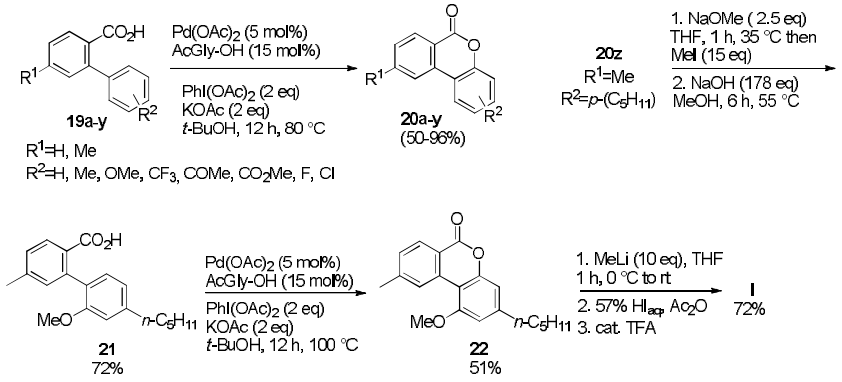
Scheme 6. Total synthesis of Didehydroconicol **V** by hyperbaric intermolecular Diels-Alder reaction and aromatization.

Bodwell and Nandularu prepared biaryl lactone esters starting from substituted salicylaldehyde **15**, dimethyl glutaconate and various ketones by a multicomponent domino reaction consisting of six reactions: Knoevenagel condensation, transesterification, enamine formation, an inverse electron demand Diels-Alder reaction, 1,2-elimination, and transfer hydrogenation reaction.[19] The authors applied this chemistry in the total synthesis of Cannabinol **I** starting from **15**. Thus, the multicomponent reaction of **15** with dimethyl glutaconate, pyrrolidine and acetone afforded chromanone **16** in 48% yield on a 1.2 g scale. This product was converted into **I** by a four-step pathway (Scheme 7) in 47% yield. The alkene **17** was obtained by a Grignard reaction of **16** with MeMgBr, followed by treatment of the crude product with *p*-TsOH (87%, two steps). Oxidative cleavage of the olefin afforded methyl ketone **18** in 57 % yield. The synthesis of Cannabinol was then completed by reacting **18** with a mixture of HI in Ac_2O, which effected both demethylation and the retro-Friedel-Crafts acylation in high yield.

The synthesis of biaryl lactones **20a-y** developed by Wang *et al.* was based on a practical Pd(II)/Pd(IV)-catalysed carbonyl-directed C–H activation/C–O cyclization reaction of biaryl carboxylic acids **19** (Scheme 8).[20] In this context, the authors carried out a concise total synthesis of Cannabinol **I** from biaryl lactone **20z** obtained in 85% yield (3.9 g scale). Thus, lactone **20z** was opened by sodium methoxide, quenched by methyl iodide, and then fully hydrolysed with sodium hydroxide to give the corresponding acid **21**. A second palladium-catalysed biaryl lactone-forming reaction furnished the biaryl lactone **22** in 51% yield. The treatment of **22** with excess MeLi, demethylation and the final cyclization of the carbinol intermediate with trifluoroacetic acid gave Cannabinol **I** in modest global yield.

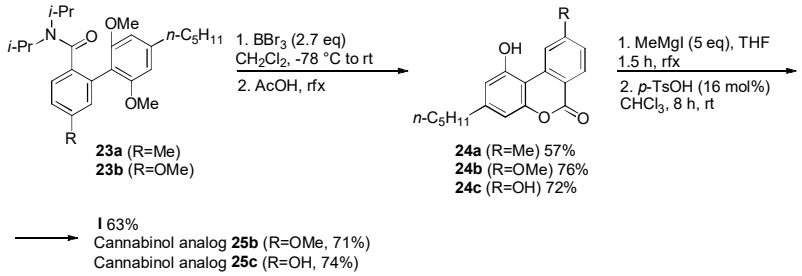


Scheme 7. Total synthesis of Cannabinol **I** through a six-reactions-domino multicomponent approach starting from substituted salicylaldehyde**15**.



Scheme 8. Double sequential Palladium-catalysed directed C–H Lactonization for the total synthesis of Cannabinol **I**.

Aside from biaryl esters, also biaryl amides could be employed to produce biaryl lactones. Makriyannis *et al*. treated the sterically hindered biaryl amides **23a-b**, prepared by a Suzuki-Miyaura cross-coupling, with BBr_3 at low temperature for the selective demethylation of the two methoxy groups of the electron-rich aromatic ring (Scheme 9).[21] Without purification, refluxing the biaryl intermediates in glacial acetic acid gave the corresponding cannabinolactone analogues **24a** and **24b** in 57 and 76% yields respectively. The methoxy group of cannabinolactone **24b** was cleaved with BBr_3 at room temperature to obtain cannabinolactone **24c** in 72% yield.

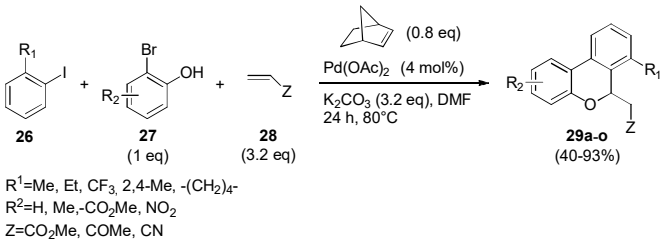


Scheme 9. Synthesis of the benzo[*c*]chromene core by intramolecular lactonization of a substituted dialkylamide.

These cannabinolactones were converted to their 6,6-dimethyl-benzo[*c*]chromenes derivatives **I** and **25b-c** by treatment with methylmagnesium bromide followed by cyclization of the tertiary alcohol intermediates with *p*-toluenesulfonic acid. Cannabinol **I** was obtained in 65% yield (Scheme 9).

3.2.Direct formation of the ether Csp^2–O or Csp^3–O linkage of the oxygenated ring

An efficient catalytic process for the synthesis of the 6*H*-benzo[*c*]chromene scaffold starting from easily available reagents was achieved by Catellani *et al.*[22] The reaction proceeds along a rather complex pathway although it is very simple from the experimental point of view, allowing for the formation of two new C–C bonds (the biaryl carbon-carbon bond and the carbon-carbon bond of the substituent in 6 position) and the oxygen-carbon bond of the pyrane ring. This multicomponent palladium-catalysed reaction occurs in a single reaction flask containing *o*-substituted aryl iodide **26**, substituted *o*-bromophenol **27**, norbornene, and the Michael acceptor **28** dissolved in DMF at 80 °C (Scheme 10). In this case, norbornene behaves as a promoter and its amount is very important for the success of the reaction. 6*H*-Benzo[*c*]chromenes **29a-o** were isolated in 40-93% yields.



Scheme 10. Multicomponent tandem Catellani/Heck/Michael reaction to furnish 6-alkyl substituted 6*H*-benzo[*c*]chromenes.

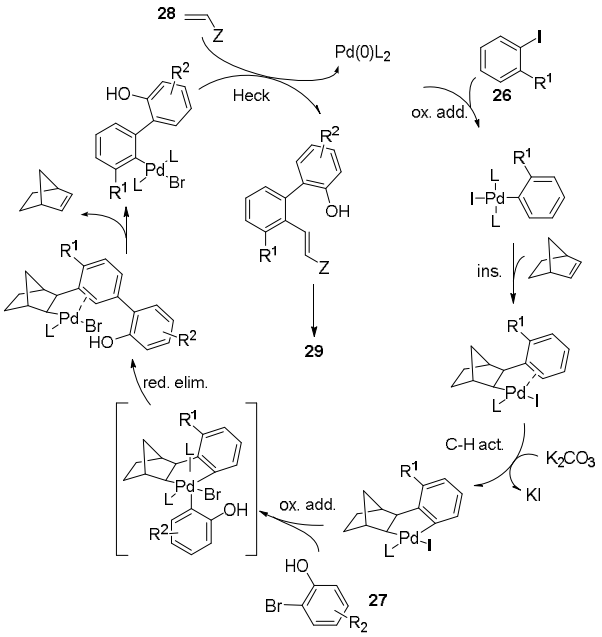
The catalytic cycle starts with the oxidative addition of the aryl iodide **26** to palladium(0) leading to an arylpalladium iodide species (Scheme 11). Stereoselective norbornene insertion give the *cis*,*exo*-arylpalladium iodide complex, in which a double bond of the aromatic ring occupies a coordination site. This weak interaction favours the formation of a new palladacycle by C–H activation. Successively, an oxidative addition of the *o*-bromophenol **27** forms a palladium(IV) intermediate complex, which, owing to steric factors, eliminates norbornene affording a biphenylpalladium complex. This complex reacts with olefin **28** according to a Heck process. The resulting vinylbiphenyl derivative undergoes an intramolecular Michael-type reaction by attack of the ortho hydroxyl group to yield the 6*H*-benzo[*c*]chromene derivative **29** in variable yields based on the employed aryl halide.

In a successive paper,[23] Catellani *et al*. demonstrated that the one-pot reaction of *o*-substituted aryl iodide **30** with 2-bromobenzyl alcohol derivative **31** under the catalytic action of Pd and norbornene, in the presence of a base, led to the 6*H*-benzo[*c*]chromene derivatives **32** (Scheme 12). Also in this case, the process first passes through a five-membered palladacycle intermediate, which controls C–C coupling, then to a seven-membered oxapalladacycle intermediate, which gives the final 6*H*-benzo[*c*]chromene by Csp^2–O coupling.

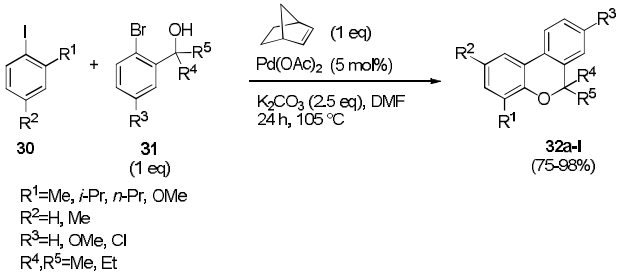
Mention should also be made of the modified protocol of Satyanarayana and co-workers, who used only tertiary bromobenzyl alcohols **33** as substrates for the construction of the biaryl structure in a domino process (Scheme 13).[24] The termination step occurred in the presence of cesium carbonate as a base and phosphines as ligands. This methodology differs from the Catellani processes because of the presence of phosphine and the absence of norbornene, the intervention of a domino homocoupling, β-carbon cleavage, and finally an intramolecular Buchwald-Hartwig cyclization to form the Csp^2–O bond of the pyrane ring. As a consequence, the 6*H*-benzo[*c*]chromenes **34a-s** were obtained in excellent yields but with the same substituents on the two benzene rings.

Li and co-workers developed a mild synthesis of the 6*H*-benzo[*c*]chromene scaffold **37** by a palladium-catalysed arylation of substituted 2-(2-iodophenoxy)-1-arylethanone **35** with variously substituted

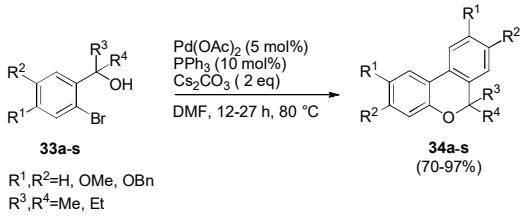
2-(trimethylsilyl)phenyltriflate **36**.[25] The reaction is believed to occur though an aryne intermediate, generated by **36** under the reaction conditions, to afford a palladium-complex intermediate (Scheme 14).



Scheme 11. Postulated mechanism for the tandem Catellani/Heck transformation for the synthesis of 6-alkyl substituted 6*H*-benzo[*c*]chromenes.

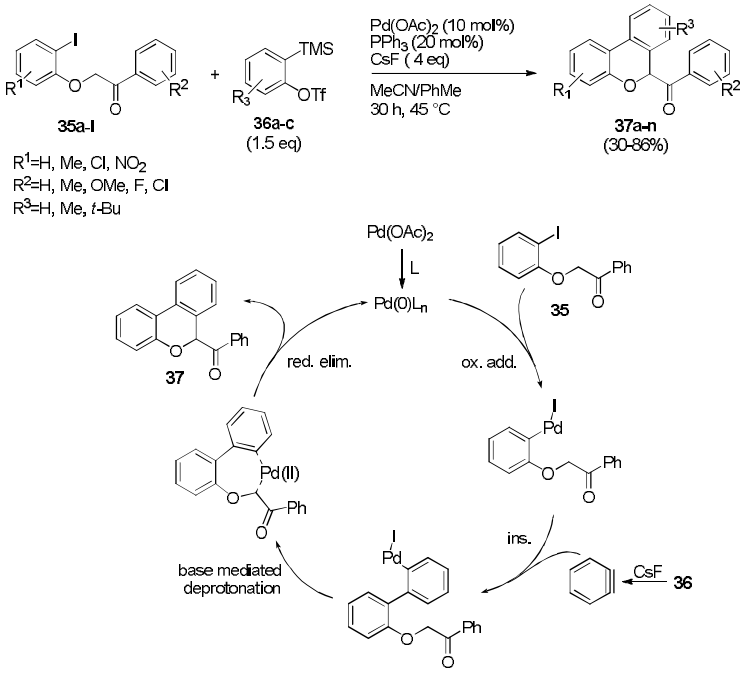


Scheme 12. Synthesis of the benzo[*c*]chromene core by a one-pot Catellani reaction of aryl iodides and 2-bromobenzyl alcohol derivatives.



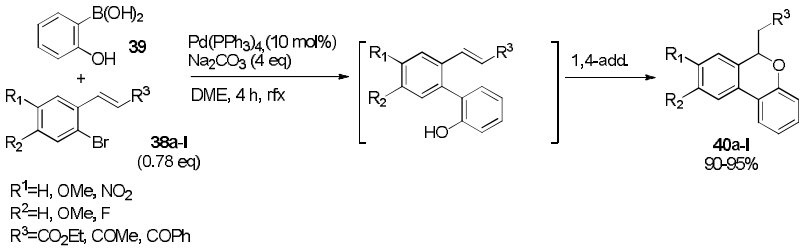
Scheme 13. Synthesis of the benzo[*c*]chromene scaffold by a palladium-catalysed homocoupling reaction of 2-bromobenzyl alcohol derivatives.

The latter then undergoes annulations on Csp^3–C atom activated by base-mediated deprotonation. This new route allows for the formation of two carbon-carbon bonds in a one-pot functionalization process providing 6*H*-benzo[*c*]chromenes **37a-n** from 30% to 86% yields. Scheme 14 also shows the possible mechanism as proposed by the authors.



Scheme 14. Palladium-catalysed aryne-iodophenoxy ether coupling to furnish 6-ketoaryl-benzo[*c*]chromenes.

A simplified and short palladium-catalysed tandem reaction of β-(2-bromophenyl)-α,β-unsaturated carbonyl compounds **38a-l** with 2-hydroxyphenylboronic acid **39** for the preparation of 6*H*-benzo[*c*]chromenes **40** was reported by Xu *et al*. (Scheme 15).[26] This strategy involves a classical Suzuki-Miyaura aryl-aryl bond formation reaction.

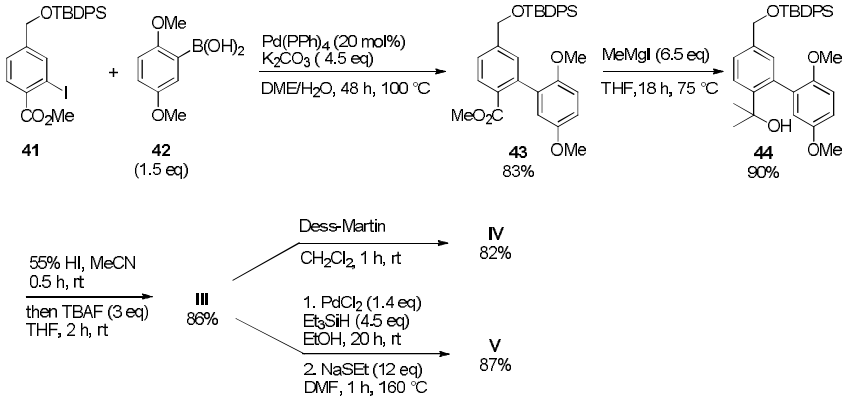


Scheme 15. Suzuki-Miyaura reaction to construct the biaryl framework followed by the formation of the pyrane ring by an oxa-Michael reaction.

Attack of the hydroxy group of the resulting biaryl intermediate at the activated olefinic carbon atom in an intramolecular Michael-type reaction allows for the formation of the Csp^3–O bond affording the

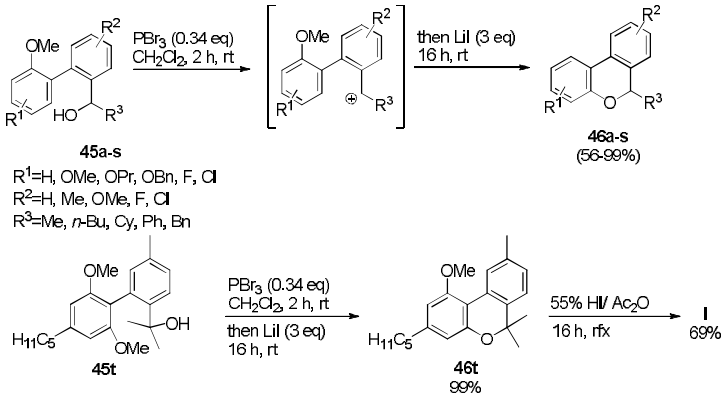
6-monosubstituted 6*H*-benzo[*c*]chromenes **40a-l** in very high yields although no substituents are present in the benzene ring fused on the [*c*]side of the chromene (Scheme 15).

Sterner and Killander developed a short total synthesis of Pulchrol **III**, Pulchral **IV**, and Didehydroconicol **V** starting with a Suzuki-Miyaura reaction of easily prepared *o*-iodobenzoate **41** with commercially available 2,5-dimetoxyphenyl boronic acid **42** to obtain the biphenyl ester **43** (Scheme 16).[27] Double addition of MeMgBr to the methyl ester **43** gave the corresponding tertiary alcohol **44** in high yield. Treatment of **44** with hydrogen iodide resulted in selective demethylation of the *o*-methoxy ether followed by acid-catalysed cyclization through the formation of C*sp*^{3}–O bond to form the crude *O*-TBDPS protected Pulchrol **III**. Then, the simple deprotection of the benzylic alcohol moiety of with TBAF gave pure Pulchrol in 64% global yield. Moreover, Dess-Martin oxidation of **III** gave Pulchral **IV** in 82% yield. Palladium-catalysed silane hydrogenation of the benzylic alcohol **III** followed by methyl ether deprotection of the intermediate furnished Didehydroconicol **V** in 87% yield.



Scheme 16. High-yielding, mild and short synthesis of the benzo[*c*]chromene-containing natural products Pulchrol **III**, Pulchral **IV** and Didehydroconicol **V**.

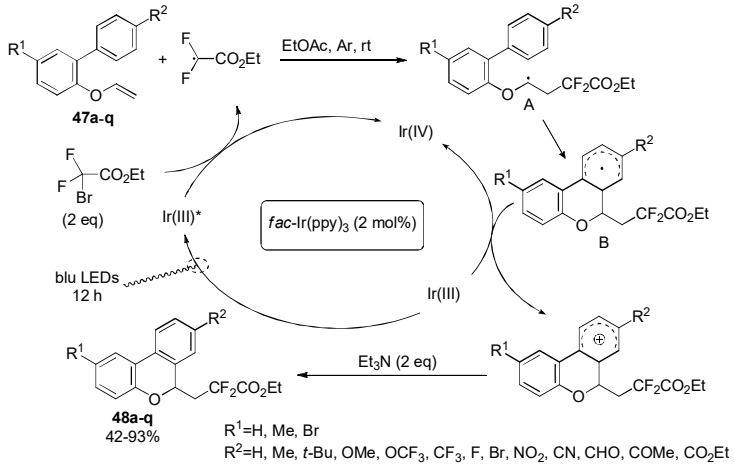
The Tummatorn *et al*. one-pot synthesis of functionalized 6-alkyl-6*H*-benzo[*c*]chromene derivatives **46a-s** involved the cyclization/selective ether cleavage of *o*-methoxybiphenyl secondary alcohol precursors **45a-s** by using PBr_3 in the presence of LiI (Scheme 17).[28]



Scheme 17. Synthesis of the benzo[*c*]chromene core by a carbocation-guided C*sp*^{3}–O bond formation. The developed method has been applied to the synthesis of Cannabinol **I**.

The required substrates were obtained by reduction of the corresponding biphenyl ketones which were synthesised by a palladium-catalysed aryl coupling. The reaction is compatible with acid-sensitive groups and the yields are excellent. S_N1 mechanism seems to be involved in the first step of the reaction to generate a benzylic carbocation intermediate, which could undergo nucleophilic substitution by a bromide ion. Then, a nucleophilic substitution of the brominated product with iodide anion provided the iodinated intermediate, which could be converted into the final product by S_N2 nucleophilic cyclization by the *o*-methoxy group with formation of methyl iodide. The authors applied the protocol to a short synthesis of Cannabinol **I** starting from biphenyl alcohol **45t**. The natural product **I** was obtained in 68% total yield (Scheme 17).

The latest use of a functionalized biaryls in the synthesis of benzo[*c*]chromenes is related to the work of Sun and co-workers[29] who proposed a novel visible-light-promoted cascade cyclization reaction initiated by intermolecular radical addition to biaryl vinyl ethers **47a-q** using easily available ethyl bromodifluoroacetate as the source of fluorinated radicals (Scheme 18). This method tolerated a wide range of functional groups providing the substituted benzo[*c*]chromenes **48a-q** in moderate to good yields. In the mechanism proposed (Scheme 18), the photoredox catalyst *fac*-Ir(ppy)$_3$ underwent a metal to ligand charge transfer process promoted by visible light to produce the excited Ir(III)*. Then the reaction of Ir(III)* with ethyl bromodifluoroacetate gives a carbon-centred difluoroacetyl radical intermediate and Ir(IV) species *via* a single electron transfer (SET). The addition of difluoroacetyl radical to the carbon-carbon double bond of vinyl ether **47** forms a new carbon centred radical **A**. Intramolecular attack of this latter radical to the arene ring produce another radical intermediate **B**,which is oxidised by the Ir(IV) species, thus regenerating the active Ir(III)-photocatalyst species for the next cycle. The subsequent deprotonation furnishes the desired product **48**.



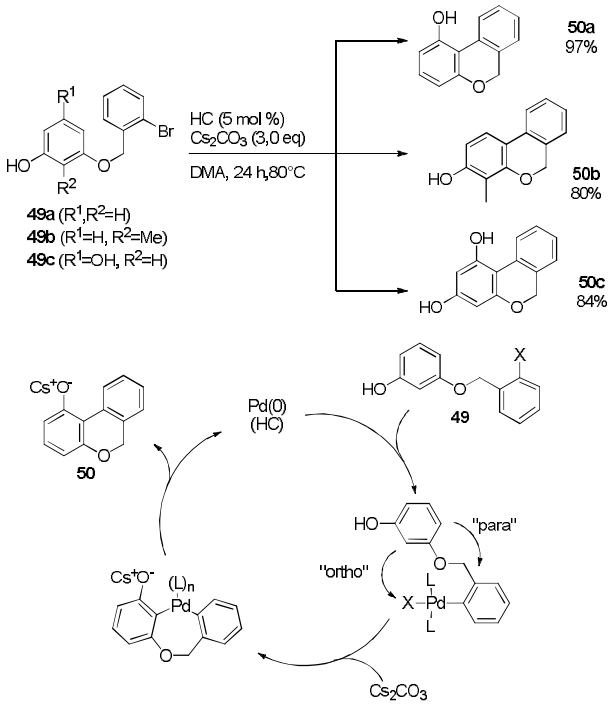
Scheme 18. Iridium-mediated photoredox radical cyclization to furnish the benzo[*c*]chromene core.

4. Starting from arylbenzyl ethers (intramolecular aryl-aryl coupling)

4.1. Metal-catalysed synthesis

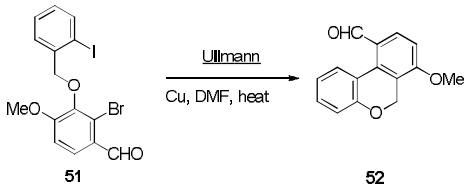
One of the most commonly reported approaches to benzo[*c*]chromenes is based on transition-metal catalysed intramolecular aryl-aryl coupling. Rawal *et al*. reported two examples of a mild and selective procedure for the palladium-catalysed intramolecular coupling of phenols with aryl halides (Scheme 19).[30] The reaction is believed to proceed *via* classical Suzuki-Miyaura catalytic cycle in which the nucleophilic sp^2 carbon is derived from the phenolate anion. First, oxidative addition of palladium(0) to the aryl bromide/iodide part of an aryl benzylether give the σ-aryl palladium intermediate, then a nucleophilic attack of the phenolate on the palladium yields, after tautomerization, a diaryl palladium species which undergoes a reductive elimination of the palladium(0) to furnish the coupling product. Good yields from 80% to 97% of

benzo[*c*]chromenes **50a-c** were obtained starting from benzyl ethers **49a-c** respectively with 5 mol% of Herrmann's catalyst (HC) and cesium carbonate in DMA.



Scheme 19. Palladium-catalysed C–H activation to form the biaryl bond from 2-bromobenzylaryl ethers.

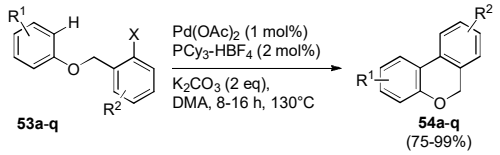
A single example of intramolecular Ullmann reaction of 2-bromo-3-(2-iodobenzyloxy)-4-methoxybenzaldehyde **51** in DMF in the presence of copper was reported by Nakazato and co-workers (Scheme 20).[31] Unfortunately, the exact reaction conditions and yield of the obtained benzo[*c*]chromene **52** were not reported.



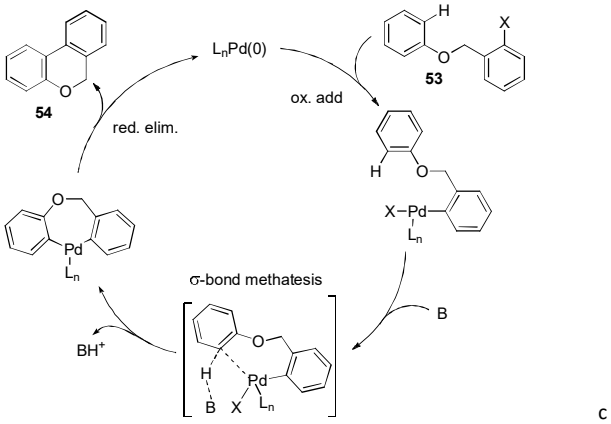
Scheme 20. Ullman-type synthesis of the tricyclic framework from 2-iodobenzylaryl ether.

A common element in classical arene coupling processes is the need for two activated arenes that can react selectively with the metal catalyst. Fagnou *et al*. proposed a palladium catalysed intramolecular direct arylation of a broad range of halobenzyl aryl ethers (Scheme 21).[32] This reaction substitutes one of the preactivated arene with a simple arene in which a Csp^2–H bond is involved in a palladium-deprotonation pathway without the need of a σ-metalorganic reagent (C–H activation). The reaction occurs in excellent yield and high selectivity giving variously substituted 6*H*-benzo[*c*]chromenes **54a-q** from halobenzyl aryl ethers **53a-q**. The Scheme 21 also shows the proposed mechanism in which the electrophilic palladation

with the formation of an arenium σ-complex, strongly supported by experimental evidences, represents the intramolecular direct arylation reaction involved.



R^1=H, *o*-Ph, *m*-*i*Pr, *m*-*t*Bu, *m*-CF_3, *m*-NO_2, *m*-CO_2Me, *m*-Cl, *m*-F, *p*-NO_2, *p*-Cl, *p*-CN, *p*-OMe
R^2=H, F, OMe
X=Cl, Br



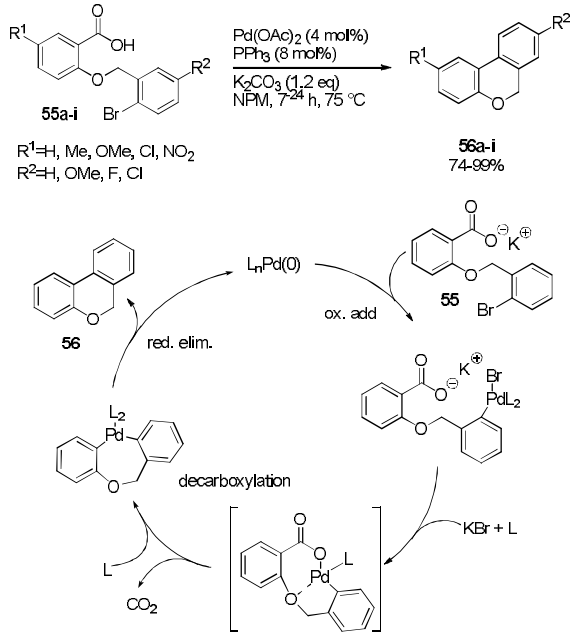
Scheme 21. Palladium-catalysed C–H activation of 2-halobenzylaryl ethers to construct the pyrane ring and proposed mechanism.

Later on, Fagnou reported an implementation of previous work in which the intramolecular direct arylation reaction could be performed under mild conditions heating to 50 °C, $Pd(OPiv)_2$ as catalyst, use of pivalic acid as an additive, and P(*p*-FPh)$_3$ as ligand.[33]

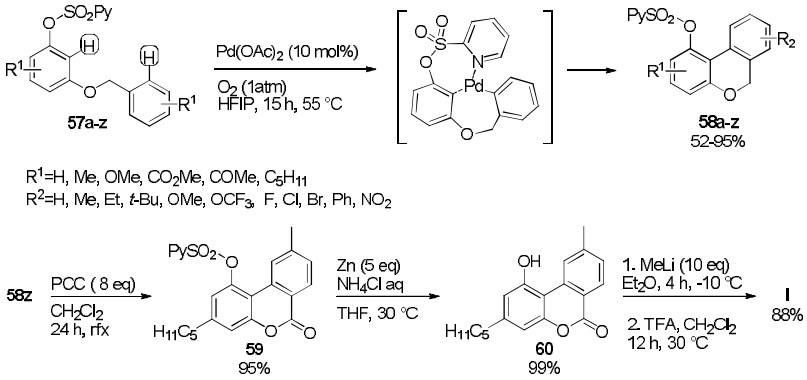
Recently, the transition-metal-catalysed decarboxylation of aromatic carboxylic acids has emerged as an alternative strategy in organic synthesis because it enables the formation of aryl-metal intermediates by loss of CO_2 making this process an alternative to perform various types of C–C and C–heteroatom bond-forming reaction. Shen *et al*. reported a new and efficient synthesis of substituted 6*H*-benzo[*c*]chromenes **56a-j** by intramolecular palladium-catalysed decarboxylative cross-coupling of arene carboxylic acids **55a-j** with aryl bromide for the construction of the biaryl motif (Scheme 22).[34] This practical and convenient method has a broad substrate scope and produce high yields of products under mild conditions. Based on previous investigations into decarboxylative coupling, a possible mechanism was proposed as outlined in Scheme 22. Furthermore, the authors reported the possibility to perform the same reaction starting from the corresponding esters of the carboxylic acids **55a-d**. In this case, lower yields of products were obtained.

The palladium-catalysed intramolecular dehydrogenative C–H/C–H coupling reaction of two simple arene of benzylaryl ethers **57a-z** to generate a series of 6*H*-benzo[*c*]chromenes **58a-z** has been reported by Wang *et al*. for the first time.[35] This approach represents an alternative to the classical cross-coupling or to the direct arylation of nonactivated aryl C–H bonds. For the success of the reaction, the substrate needs an appropriate directing group and, after a brief screening, the authors identified the *O*-(2-pyridyl)sulfonyl group as the optimal one. This moiety acts both as the protecting group for the hydroxyl and as the directing group to facilitate the formation of the phenyl-palladium complex, obtained through the electrophilic

substitution of the *ortho* C–H bond of the phenol (Scheme 23). The coupling was performed with molecular oxygen as the terminal oxidant, but it was necessary to employ HFIP as solvent. The reaction has a broad substrate scope, good tolerance of functional groups and efficiency (52-95% yields). An efficient total synthesis (86% yield) of Cannabinol **I** from a 6*H*-benzo[*c*]chromene **58z** was reported by the authors.



Scheme 22. Palladium-catalysed decarboxylative coupling of a salicylic acid-2-bromobenzyl ether.

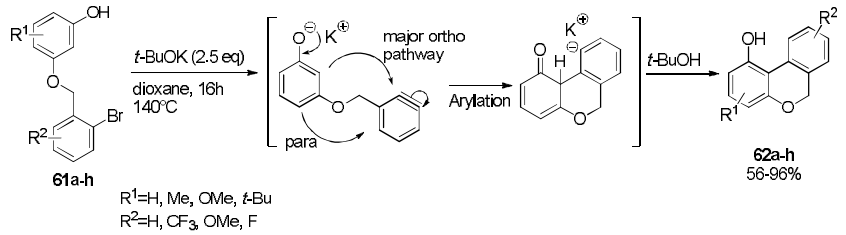


Scheme 23. Construction of the 6*H*-benzo[*c*]chromene scaffold by a pyridinesulfonate-directed dehydrogenative C–H/C–H coupling of arylbenzyl ethers catalysed by Palladium.

4.2. Transition-metal-free synthesis

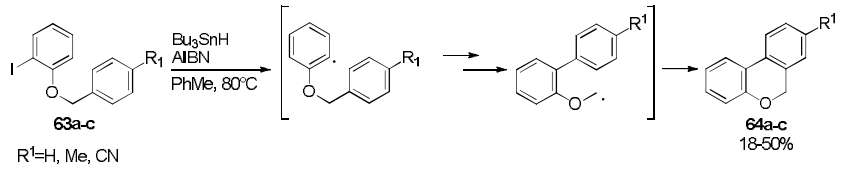
Daugulis and Bajracharya developed a direct transition-metal-free, base-mediated intramolecular arylation of phenols with aryl bromides in the presence of an excess of ^{t}BuOK in dioxane at 140 °C (Scheme 24).[36] Thus, the intramolecular cyclization of 3-(2-bromobenzylooxy)phenols **61a-h** afforded the corresponding 6*H*-benzo[*c*]chromenes **62a-h** in good to excellent yields as a mixture of regioisomers. The

reaction probably proceeds by an initial formation of a benzyne intermediate (generated from aryl bromide in the presence of base) followed by a formal base-mediated C–H activation to give a reactive intermediate enolate which undergoes the arylation process. In all cases, arylation ortho to the phenolate is the major reaction pathway.



Scheme 24. Base-catalysed direct arylation of phenols through the formation of a benzyne intermediate.

Low yields of three 6*H*-benzo[*c*]chromenes **64a-c** were obtained by Harrowen *et al.* through an intramolecular ipso-substitution reaction initiated by the intramolecular addition of an aryl radical to a benzyl ether (Scheme 25).[37] The authors hypothesised that the (2-iodoaryl)benzyl ether **63**, under standard radical-forming conditions (treatment with tributyltin hydride and AIBN), gives the corresponding aryl radical, which cyclizes in a 5-*exo*-trig mode to furnish a spirocyclic radical intermediate. Then, the fragmentation of this intermediate creates the new aryl-aryl bond and re-establishes the aromaticity. The newly obtained *O*-methyl radical can give a tricyclic radical to form **64** or can undergo fragmentation to the biaryl derivative. The detailed reaction conditions were not reported.

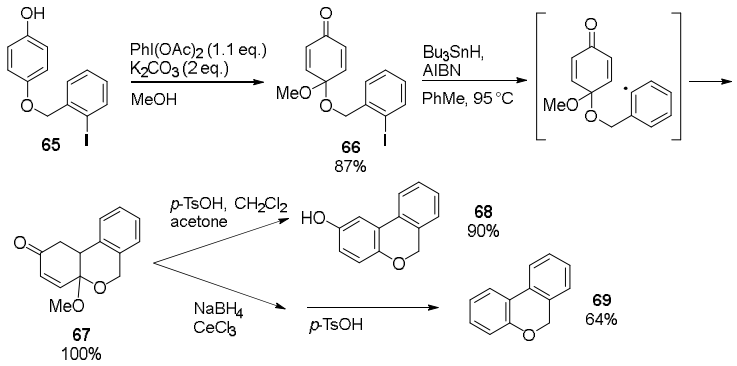


Scheme 25. Cascade radical pathway to the benzo[*c*]chromene tricyclic core starting from 2-iodophenoxybenzyl ethers.

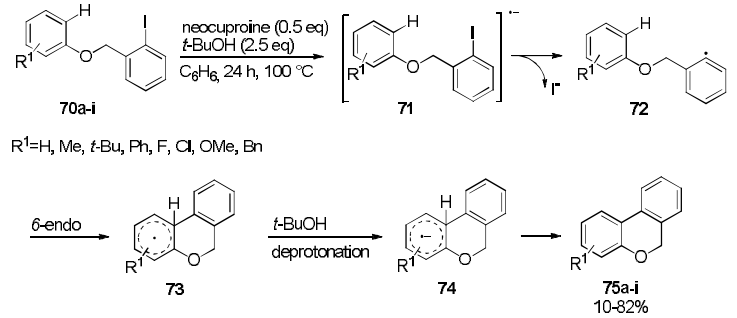
Clive and co-workers prepared two 6*H*-benzo[*c*]chromenes **68** and **69** by a formal radical cyclization onto the benzene ring of arylbenzyl ether **65** (Scheme 26).[38] First, ether **65** was dearomatized and transformed into a cross-conjugated dienone **66**, which readily undergoes radical cyclization in the presence of allyltributyltin or tributyltin hydride. This leads to an intermediate that is easily cyclized to **67**. Upon aromatization with *p*-TsOH, hydroxy-substituted 6*H*-benzo[*c*]chromene **68** was obtained in excellent yield. Reduction of ketone **67** gave a single alcohol which after aromatization furnished **69** in good yield. Unfortunately, the exact reaction conditions were not reported.

A simple, one-step synthesis of monofunctionalized 6*H*-benzo[*c*]chromenes **75a-i** was realized by Shi *et al*. starting from (2-iodobenzyl)arylethers **70a-i** by intramolecular homolytic aromatic substitution avoiding the use of transition metal catalysts (Scheme 27).[39] In this case, the authors hypothesized that the complex of potassium *tert*-butoxide with neocuproine is a radical precursor. After a single electron transfer (SET) process with **70**, a radical anion**71** is generated, which further undergoes dehalogenation to generate an aryl radical **72** that initiates the cyclization process. A 6-*endo* intramolecular aromatic substitution occur directly to produce the new radical **73** or *via* a rearrangement of the 5-*exo* product intermediate. After deprotonation with the assistance of *t*-BuOK, another radical anion **74** is generated. Then a radical chain transfer occurs between **74** and substrate **70**, resulting in the formation of product **75** and regeneration of radical anion **71**. 6*H*-Benzo[*c*]chromenes **75a-i** were obtained in good to excellent yields. The authors tested

aryl bromides too. Compared with the corresponding aryl iodides, most of the aryl bromides reacted in relative lower yields indicating their lower reactivity in such radical process.



Scheme 26. Dearomative oxidation and radical cyclisation of 1,4-diphenol derivatives to give the unsubstituted benzo[*c*]chromene core.



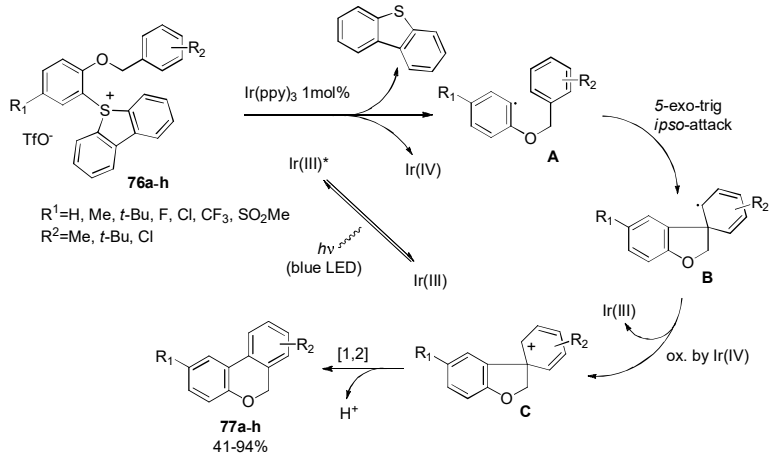
Scheme 27. Radical cyclization of (2-iodobenzyl)aryl ethers mediated by a neocuproine-*t*BuOK complex.

Another elegant method was recently reported by Alcarazo and co-workers who used *S*-aryl dibenzothiophenium salts **76a-h** as radical precursors, which were easily prepared by sulfenilation at the *ortho* position of the phenol moiety of *p*-alkyl-substituted aryl benzylethers (Scheme 28).[40] The reaction starts with a photocatalytically-triggered single-electron transfer to the sulfonium salt, which promotes the formation of an aryl radical A *via* selective mesolitic cleavage of the S-Ar_{exo} bond. Mechanistic studies revealed that this initial radical species cyclizes to intermediate **B** following a kinetically favoured 5-*exo*-trig pathway. Subsequently, the reaction preferentially proceeds *via* the oxidation of **B** into carbocation **C**, followed by ring expansion through [1,2]-aryl rearrangement. Deprotonation, favoured by the rearomatization of the cationic intermediate, delivers **77**. 6*H*-Benzo[*c*]chromenes **77a-h** were obtained under mild conditions and with yields ranging from 41% to 94% (Scheme 28).

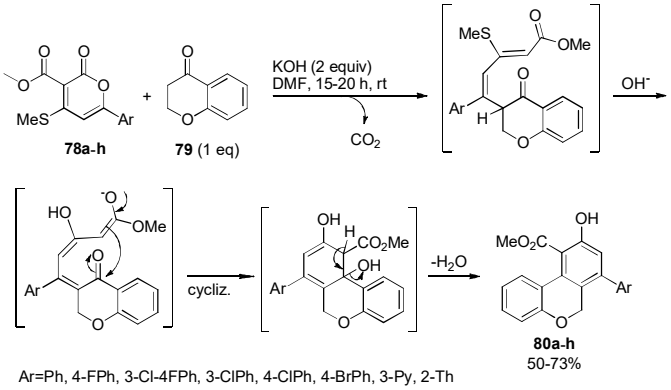
5. Annulation reaction to benzene ring on the [*c*] side of a chromene system

The first example of an annulation reaction employed for the construction of a benzene ring onto the side [*c*] of chroman-4-one was reported by Ram *et al.* in 2001.[41] This approach to the synthesis of 6*H*-benzo[*c*]chromenes is based on the base-catalysed ring-transformation reaction of 6-aryl-3-carbomethoxy-4-methylthio-2*H*-pyran-2-ones **78a-h** and chroman-4-one **79** (Scheme 29). Thus, the carbanion generated *in situ* from chroman-4-one **79** attacks **78** with ring opening and decarboxylation, followed by condensation-cyclization on the keto functionality of **79** with elimination of water. This reaction furnished 6*H*-benzo[*c*]chromenes **80a-h** under mild reaction conditions, with the use of inexpensive

reagents, and with moderate to good yields. Unfortunately, the products **80** do not have any substituents on the other benzene ring.

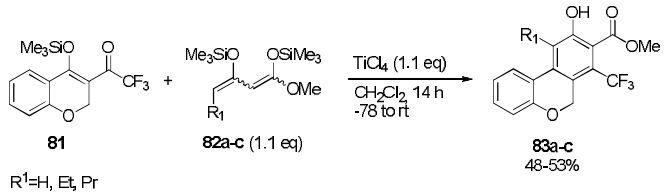


Scheme 28. Iridium-catalysed photochemical cyclization of arylthianthrenium salts.



Scheme 29. Base-catalysed annulation of chromen-4-ones and 3-carboxy-substituted 2*H*-pyranones.

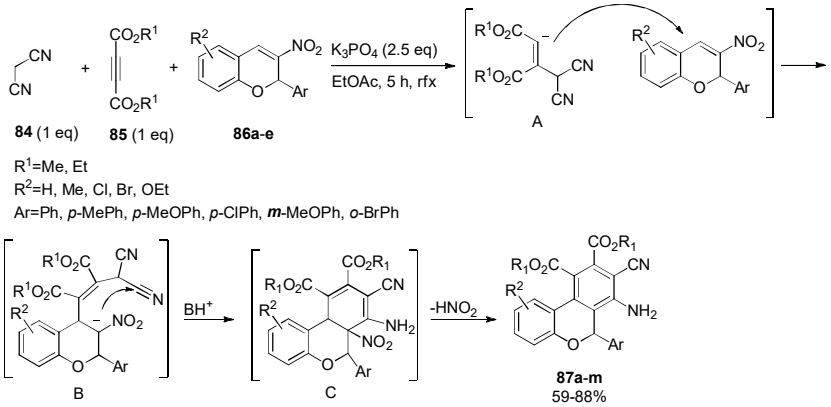
Langer and co-workers prepared some trifluoromethyl-substituted 6*H*-benzo[*c*]chromenes **83a-c** with modest yields. The reaction is based on a formal [3+3]-cyclocondensation of the fluorinated chromene derivative **81** and 1,3-bis(silyloxy)-1,3-butadienes **82**(Scheme 30).[42]



Scheme 30. Synthesis of 7-CF_3-substituted benzo[*c*]chromenes by the annulation reaction of 3-trifluoroacetyl-substituted chromenone **81** and the electron-rich dienes **82**.

The reaction proceeds with high regioselectivity due to the attack of the carbon atom in 2 position of the diene **82** to the carbonyl group of **81**. Also in this case, the products **83** do not have any substituents on the second benzene ring (Scheme 30).

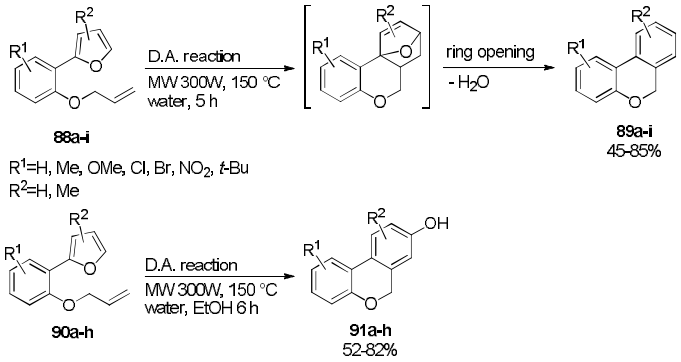
An efficient and K_3PO_4-promoted three-component reaction allowed Yan *et al*. to obtain highly functionalized 6*H*-benzo[*c*]chromenes **87a-m** in good to excellent yields (Scheme 31).[43] The plausible reaction mechanism proposed by the authors involves an initial base-promoted deprotonation of malononitrile **84** to give the corresponding carbanion. The newly formed nucleophile attacks the dialkyl but-2-ynedioate **85** to form a second carbanion intermediate **A**, that is able to react with 2-aryl-3-nitrochromene **86** in a Michael-type reaction forming the carbanion **B**. Its intramolecular attack onto one of the cyano groups produces a cyclized intermediate **C** which, after protonation, tautomerization, and elimination of the nitro group, produced the 6*H*-benzo[*c*]chromenes **87a-m** in 59 to 88% yields.



Scheme 31. Tandem double Michael followed by cyclization to furnish the 6-aryl-benzo[*c*]chromenes.

6. Simultaneous formation of the pyranic and benzene ring *via* intramolecular Diels-Alder reaction

The catalyst-free intramolecular Diels-Alder reaction with a furan moiety as the diene partner has been employed by Fan *et al*. as a valuable tool for the synthesis of the 6*H*-benzo[*c*]chromene scaffold using water or a water/ethanol mixture as green reaction medium (scheme 32).[44]

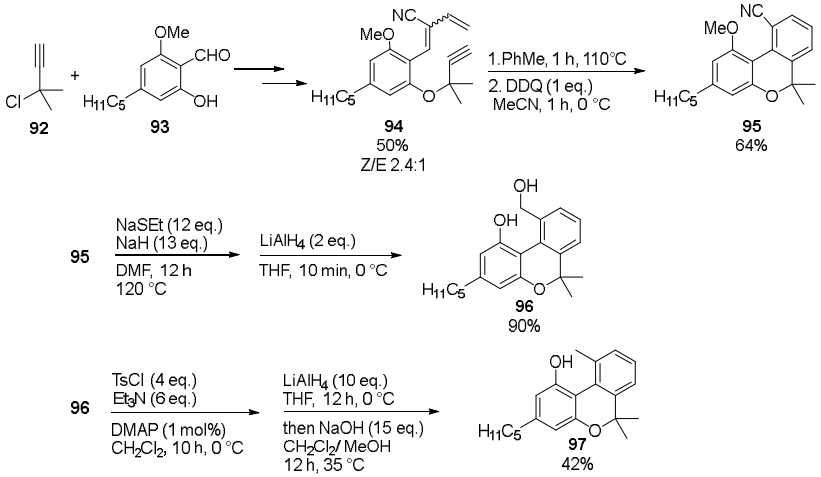


Scheme 32. Microwave-assisted synthesis of benzo[*c*]chromenes *via* an intramolecular Diels-Alder reaction between the furan ring and the allyl moiety.

Although furan is a relatively unreactive diene partner toward unactivated alkenes for the Diels-Alder reaction, the authors found that the reaction of substituted 2-(2-allyloxy)phenyl)furans **88a-i** in water, at 150

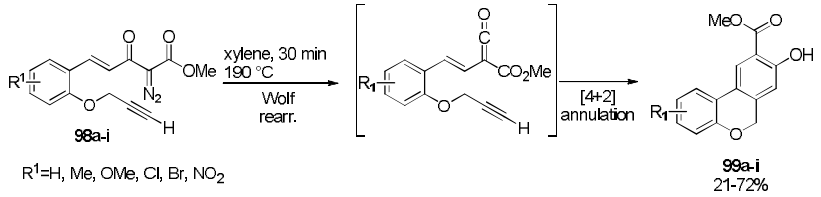
°C, and in a sealed vessel produced 6*H*-benzo[*c*]chromenes **89a-i** through ring-opening of the oxabicyclic cycloadduct intermediates and subsequent dehydrative aromatization. Various functional groups such as methoxy, bromo and nitro were tolerated. In addition, the propargyl analogue 2-(2-(prop-2-ynyloxy)phenyl)furans **90a-h** reacted under similar synthetic conditions to furnish the corresponding 6*H*-benzo[*c*]chromen-8-ol derivatives **91a-h** in good to excellent yields (Scheme 32). In both cases, the necessary substrates were prepared by a four-steps transition metal-catalysed process.

Grenning and co-workers reported a four-step synthesis of an unnatural isomer of Cannabinol **95** from salicylaldehyde **93** and propargyl chloride **92** by an intramolecular Diels-Alder reaction between the substituted benzene **94** intermediate containing a diene and an alkynyl function (Scheme 33).[45] The Diels-Alder reaction, performed in a pressure flask at 110 °C, gave the functionalized 6*H*-benzo[*c*]chromene **95** in 64% yield. This compound was used as a useful starting point for further structural elaborations. Thus, the 10-hydroxymethyl derivative **96** was obtained after demethylation and reduction of the lactone intermediate whereas compound **97**, the C-10 isomer of natural CBN, was accessed by two steps benzylic reduction of **96**.



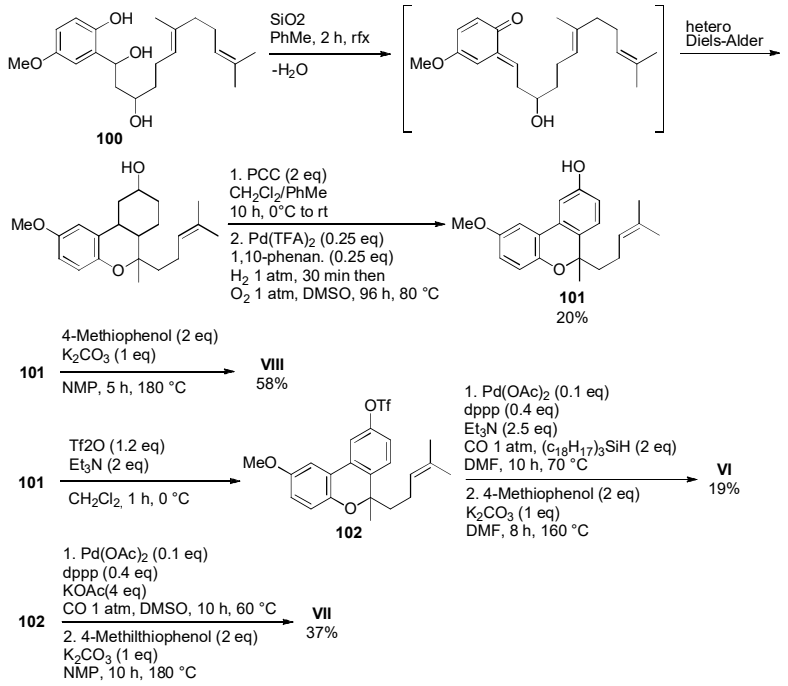
Scheme 33. Access to the 10-substituted non-natural isomers of Cannabinol and 9-hydroxymethyl Cannabinol by intramolecular Diels-Alder.

A unique, functional group tolerant, and thermally-induced intramolecular [4+2]-annulation of diazoacetate enones **98a-i** tethered with unactivated alkynes has been developed by Xu *et al.* for the synthesis of functionalized 6*H*-benzo[*c*]chromenes **99a-i** (Scheme 34).[46] The reaction proceeds in moderate to good yields through a Wolff rearrangement with dinitrogen as the only byproduct to afford an intermediate vinyl ketene, which reacts as an electron-rich diene to furnish the target compounds after tautomerization of the intermediate cycloadduct.



Scheme 34. Tandem Wolff rearrangement/intramolecular Diels-Alder reaction for the synthesis of 8-hydroxy-9-carboxy-benzo[*c*]chromenes.

Zhao and co-workers developed a divergent synthesis of Ganocochlearin C **VI**, Ganocochlearin D **VII**, and Cochlearol T **VIII** from a common 6*H*-benzo[*c*]chromene intermediate **101** (Scheme 35).[47] Key reactions to this synthesis are an intramolecular hetero-Diels-Alder reaction and Stahl-type oxidative aromatization, allowing for the formation in low yield of the 6*H*-benzo[*c*]chromene intermediate **101** starting from linear triol **100**. Then, after highly selective late-stage transformations, this approach resulted in the first total synthesis of Ganocochlearin C, Ganocochlearin D, as well as Cochlearol T. Demethylation of **101** with 4-methyl thiophenol in NMP at 180 °C afforded **VIII** in moderate yield. The triflation of **101** with Tf_2O gave the triflate **102** which reacted in a palladium-catalysed formylation to provide an aldehyde intermediate. The latter, after demethylation, afforded **VI** in 19% yield after 3 steps. On the other hand, palladium-catalysed carboxylation of the triflate **102** and subsequent demethylation gave **VII** in 59% yield after two steps.



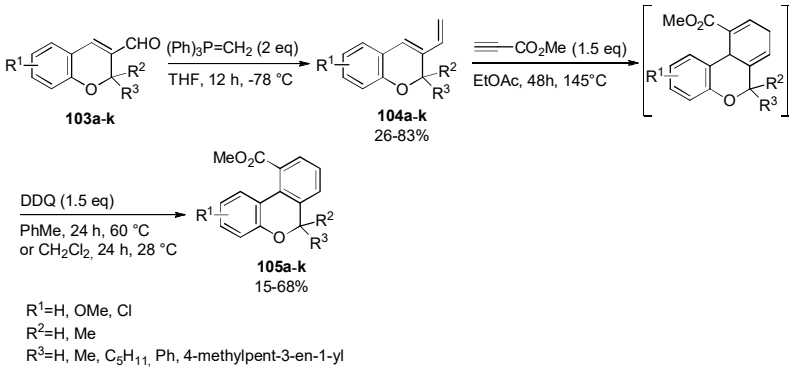
Scheme 35. Divergent synthesis of Ganocochlearin C **VI**, Ganocochlearin D **VII**, as well as Cochlearol T **VIII** based on a late-stage functionalization of the common intermediate **101**.

7. Substituted 6*H*-benzo[*c*]chromenes via an intermolecular Diels-Alder reaction

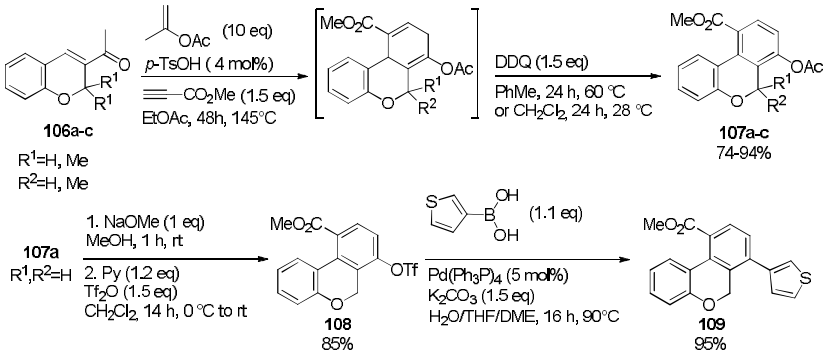
In 2021 Temperini *et al.* reported a new and metal-free approach to the synthesis of substituted 6*H*-benzo[*c*]chromenes **105a-k** in a three-step synthetic sequence starting from variously substituted 2*H*-chromene-3-carbaldehydes **103a-k** (Scheme 36), which were obtained in good to excellent yields by a domino oxa-Michael/Aldol condensation.[48] A Wittig reaction transformed **103a-k** into 3-vinyl-2*H*-chromenes **104a-k**. Then, a novel and highly regioselective intermolecular Diels-Alder cycloaddition between **104a-k** and methyl propiolate, followed by oxidative aromatization of the cyclohexadiene cycloadduct intermediates, furnished the final 6*H*-benzo[*c*]chromene **105a-k** in moderate to good yields (up to 68% over two steps).

Furthermore, a multicomponent one-pot acetylation/intermolecular Diels-Alder protocol was employed by the same authors to expand the set of the accessible 6*H*-benzo[*c*]chromenes (Scheme 37). In this reaction, a diene was generated *in situ* by *p*-TsOH-catalysed acetylation of ketones **106a-c** with

isopropenyl acetate. The enol acetate diene intermediates underwent the Diels-Alder cycloaddition with methyl propiolate to give the cyclohexadiene cycloadduct intermediates, which after oxidative aromatization, furnished the corresponding 7-acetoxy-6*H*-benzo[*c*]chromenes **107a-c** in excellent yields (74-94%) as the sole regioisomers. Late-stage functionalization of 6*H*-benzo[*c*]chromene **107a** was also proposed by the authors. Thus, a chemoselective deprotection by transesterification with sodium methoxide in methanol at room temperature afforded the free phenol intermediate, which was further converted into the corresponding triflate ester **108**. This compound was an ideal substrate to perform a Suzuki-Miyaura reaction, producing the 7-heteroarylated cross-coupling product **109** in 81% global yield.



Scheme 36. Diels-Alder/oxidative aromatization reaction sequence for the synthesis of substituted 6*H*-benzo[*c*]chromenes from easily accessible 3-formyl-chromenes.



Scheme 37. Multicomponent approach to access 7-acetoxy- and 7-heteroaryl-substituted 6*H*-benzo[*c*]chromenes.

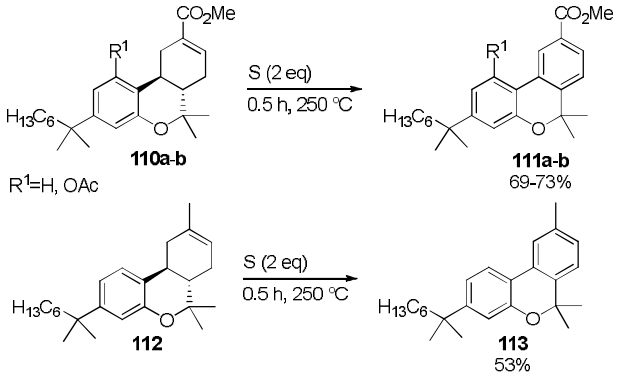
8. Other synthetic paths

Beside the several synthetic strategies discussed above, the aromatization of natural, semisynthetic, and totally synthetic tetrahydrocannabinols could be another way to prepare 6*H*-benzo[*c*]chromenes. Razdan *et al.* synthesized the 6*H*-benzo[*c*]chromenes **111a-b** by dehydrogenation with sulphur of the corresponding synthetic Δ^8-THC analogue compounds **110a-b** (Scheme 38).[49] Using the same procedure, 6*H*-benzo[*c*]chromenes **113** was obtained from **112**.

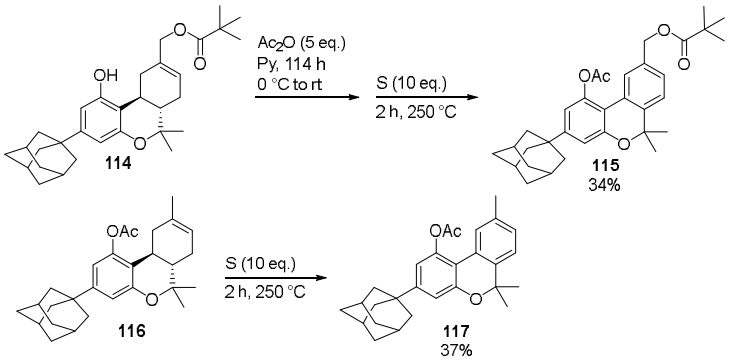
Similarly, Makriyannis and co-workers aromatized the synthetic tetrahydrocannabinols **114** and **116** into 6*H*-benzo[*c*]chromenes **115** and **117** respectively and in good yields (Scheme 39).[10]

Finally, Deiters and Teske proposed a regioselective and efficient synthetic route to the 6*H*-benzo[*c*]chromene core structures **118a-c**, based on a regioselective ruthenium-catalysed

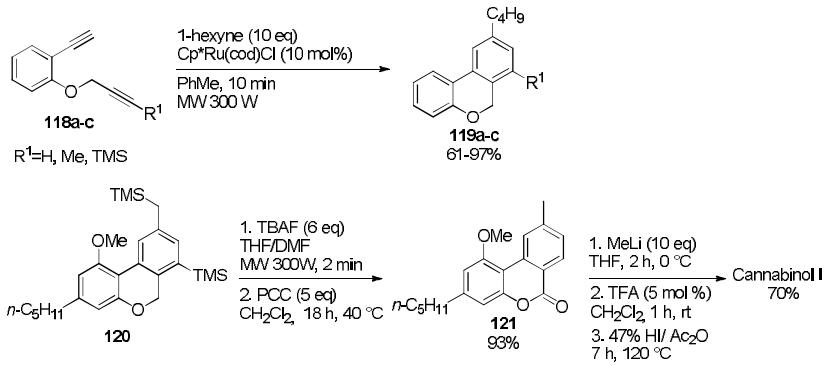
microwave-mediated [2+2+2]-cyclotrimerization reaction from accessible alkyne precursors **119a-c** with 1-hexyne (Scheme 40).[50] The natural compound Cannabinol **I** was also synthesized in 65% total yield from 6*H*-benzo[*c*]chromene **120** through the lactone intermediate **121** to illustrate the flexibility of the approach proposed.



Scheme 38. Dehydrogenative aromatization of Δ^8-THC analogues to furnish the corresponding 6*H*-benzo[*c*]chromenes.



Scheme 39. Synthesis of 3-adamantyl substituted 6*H*-benzo[*c*]chromenes through an oxidative aromatization of Cannabinol derivatives **114** and **116** employing sulphur.



Scheme 40. Ru-catalysed microwave-assisted cyclotrimerization of alkynes to furnish 6*H*benzo[*c*]chromenes.

9. Conclusion

The 6*H*-benzo[*c*]chromene core is a prominent scaffold for the synthesis of both natural products and biologically relevant molecules and it also finds potential applications in materials science. A general overview of the currently published synthetic methodologies for its synthesis has been given, identifying several different disconnection approaches. Although the proposed strategies are plentiful, most of them rely on transition metal-mediated chemistry to construct the tricyclic core. However, these methodologies require further careful purification steps to remove the remaining metal traces for their successful employment in larger scale pharmaceutical and optoelectronic applications. Some greener synthetic approaches that do not involve transition metal catalysis have been described as well, showing comparable results to the metal-mediated ones. Taken together, the currently available synthetic strategies allow for the preparation of a wide range of substituted 6*H*-benzo[*c*]chromenes for both pharmaceutical and optoelectronic applications, but there is still ample room for research towards a more optimal synthetic route.

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