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TOTAL SYNTHESIS OF COLCHICINE ALKALOIDS

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1. Introduction to N-acetylcolchinol and allocholchicinoids. The Colchicum plant had been used for the treatment of gout in ancient Greece for over two millennia before the active species colchicine (Figure 1, 1) was found and extracted from Colchicum for the first time by Pelletier and Caventou in 1820.1 It took more than 100 years for researchers to determine its structure. Dewar suggested that colchicine contained two 7-membered rings,2 and later King and co-workers determined the structure of colchicine was established by X-ray crystallography.3 The first total synthesis of colchicine was accomplished by Eschenmoser in 1959.4 Nowadays, colchicine is a well-known pseudo-alkaloid that has been widely used to treat gout, immune-mediated diseases, and psoriatic arthritis.5 It was shown to inhibit leukocyte-endothelial cells and T-cells by binding to intracellular tubulin monomers, which prevents their polymerization.6 Thus, colchicine has the potential to inhibit cancer cell growth, but it proved to be toxic to normal cells. Instead, a less toxic to mammalian cells demecolcine 2), where the acetyl group on the amino group is replaced with methyl, is used in chemotherapy.

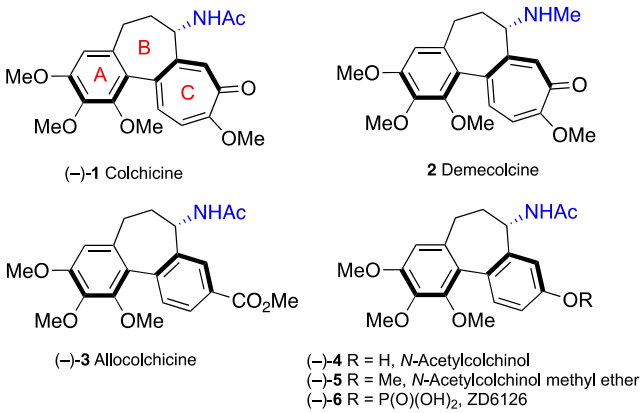


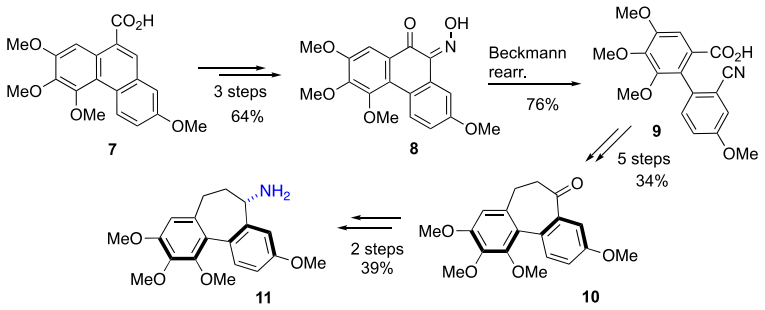
Figure 1. Colchicine **1** and its analogues **2-6**.

More recently, colchicine showed some positive effects as a potential treatment for COVID-19 due to its anti-inflammatory properties.[7] Investigation of colchicine analogues revealed that allocolchicinoids derivatives where the 7-membered tropolone ring was replaced with a benzene ring (**3**–**6**) showed good biological activity and less toxicity compared to the parent colchicine.[8] *N*-Acetylcolchinol **4** is a known tubulin polymerisation inhibitor; its water-soluble phosphate ZD6126 **6** was developed as the prodrug,[9] which in vivo is converted into the active *N*-acetylcolchinol **4**. ZD6126 selectively induced tumour vascular damage and tumour necrosis at well-tolerated doses in animal models, but it was found to be toxic to humans and, therefore, was discontinued. However, the pronounced biological activity of colchicine alkaloids helped to maintain a sustained interest in this class of compounds, thus fueling the need for a robust methodology to access their synthetic analogues. The review is divided into two main chapters. The first will cover the diverse strategies for assembling the tricyclic core of the colchinoids apart from the methods based on the arene-arene coupling to create ring B, while the second chapter will focus on the strategies centred on these intramolecular aromatic cross-coupling methods.

2. Synthetic strategies employed for the construction of the tricyclic core of *N*-acetylcolchinol and analogues.

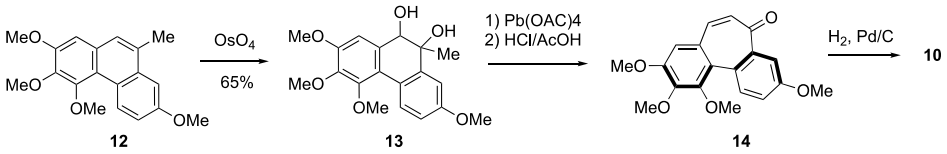
In mid 20th century, the first approaches to the synthesis of *N*-acetylcolchinol methyl ether **5** were reported, where the 7-membered ring of the colchinol core was constructed by the sequence of reactions involving oxidative scission of the respective phenanthrene derivatives. Rapoport and Cisney reported the first total synthesis of racemic colchinol methyl ether from 2,3,4,7-tetramethoxyphenanthoic acid **7**.[10,11] This was converted in three steps to monoxime **8** and then to cyanoacid **9** by Beckmann rearrangement (Scheme 1). Intermediate dihydrotropone **10** was achieved in five steps from **9**. This synthetic route gave racemic colchinol methyl ether **11** in 4.5% overall

yield over 13 steps. Chiral resolution of **11** with *D*-tartaric acid afforded free amine crystalline salt and the subsequent acetylation of the primary amine gave rise to (–)-*N*-acetylcolchinol methyl ether (–)-**4**.



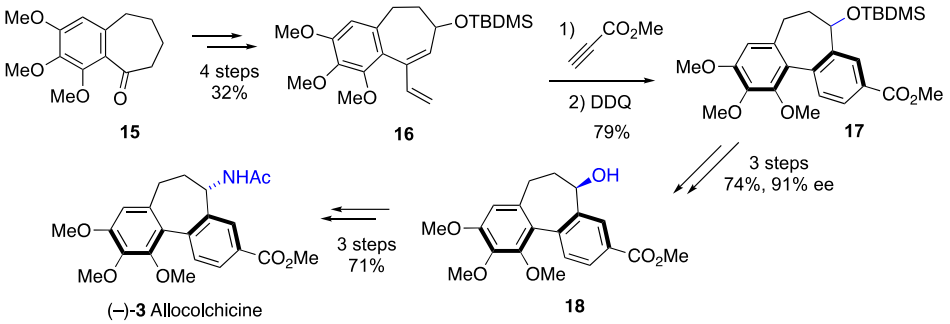
Scheme 1.

At approximately the same time, Cook reported a synthetic sequence towards the same dihydrotropone **10** starting from 2,3,4,7-tetramethoxy-9-methyphenanthrene **12** (Scheme 2).[12] In their approach, the dihydroxylation of **12** afforded **13**. Treatment of **13** with lead tetraacetate cleaved the vicinal diol followed by intramolecular aldol condensation under acidic conditions to form tropone derivative **14**, which was hydrogenated over palladium on carbon to ketone **10**. The reductive amination, chiral resolution and acetylation sequence similar to the one described in Scheme 1 afforded the target (–)-*N*-acetylcolchinol methyl ether (–)-**4**.



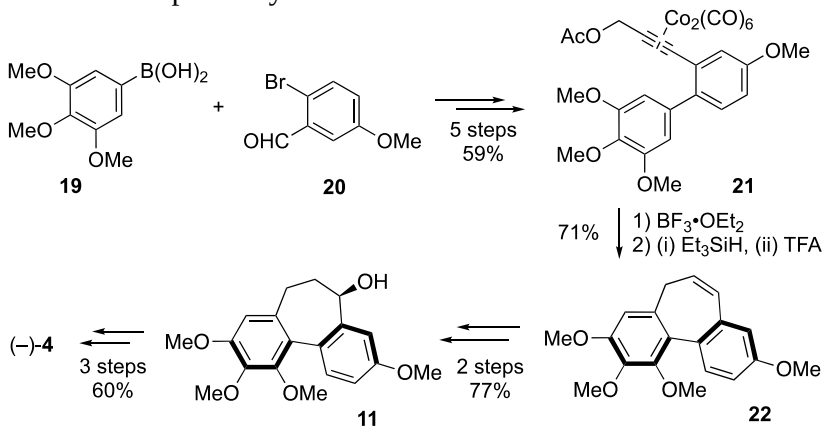
Scheme 2.

A different strategy was introduced by Wulff and co-workers that centred on a Diels-Alder cycloaddition to assemble the methyl benzoate ring of allocolchicine **3**, followed by aromatization (Scheme 3).[13] The Diels-Alder diene **16** was prepared from known benzosuberone **15** in 4 steps. Cycloaddition with methyl propiolate gave the tricyclic core followed by DDQ oxidation to afford **17** in 79%. Deprotection of the TBDMS, oxidation of the resulting alcohol to ketone and asymmetric reduction with (+)-TarB-NO_2/$LiBH_4$ produced enantioenriched alcohol **18** in 91% *ee* and 74% yield over 3 steps. The target (–)-allocolchicine **3** was achieved in further 3 steps which included Mitsunobu substitution of the hydroxyl with azide, followed by hydrogenation and acetylation.



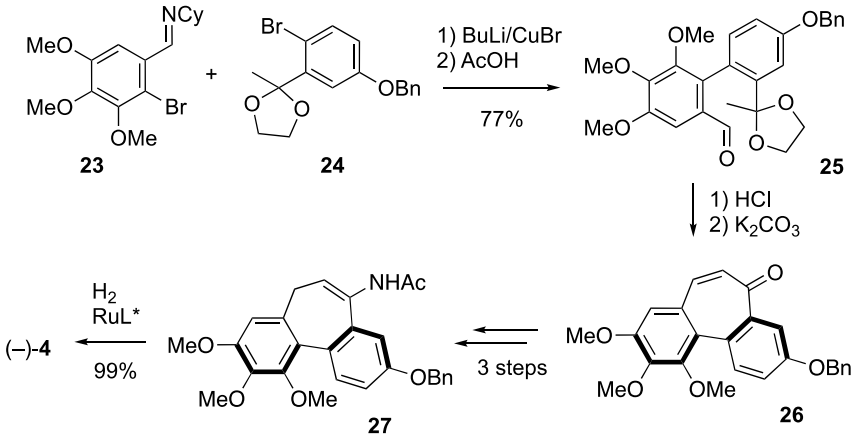
Scheme 3.

A different approach was reported by Green.[14] Construction of the biaryl precursor **21** involved Suzuki coupling of commercial starting materials **19** and **20** followed by Corey-Fuchs protocol and then the formation of cobalt complex **21** (Scheme 4). Treatment of **21** with Lewis acid furnished the tricyclic colchinoid core. Decomplexation was accomplished by hydrosilylation with Et_3SiH followed by desilylation by TFA to give **22**. Hydroboration and oxidation on the double bond gave alcohol **11**. The rest of the synthesis followed the protocols described by Wulff (Scheme 3);[13] the overall yield of this 11-step total synthesis was 18%.



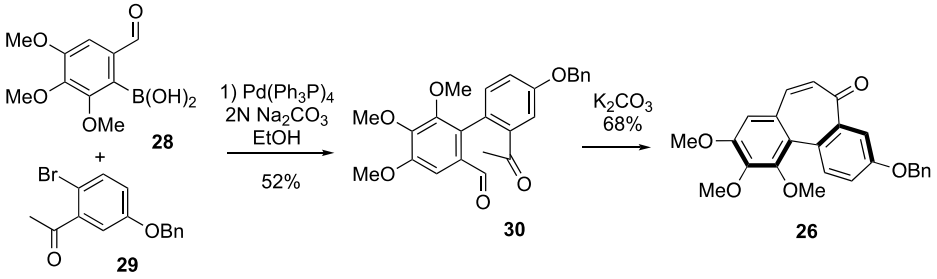
Scheme 4.

Synthesis of a water-soluble pro-drug (-)-**6** ZD6126 was reported by Astra-Zeneca (Scheme 5).[15] In this strategy, precursors **23** and **24** were obtained in 2 and 3 steps, respectively, from commercial reagents. Then, they were joined together through a Cu-mediated Ullmann-type coupling to give **25** in 77% yield. Ring B was installed by aldol reaction after deprotection of ketone in **25** to afford tropone **26**, which in three steps was converted to enamide **2**, followed by catalytic enantioselective hydrogenation using ruthenium/(*S*)-isopropyl-ferroTANE to afford (–)-**4** (Scheme 5).



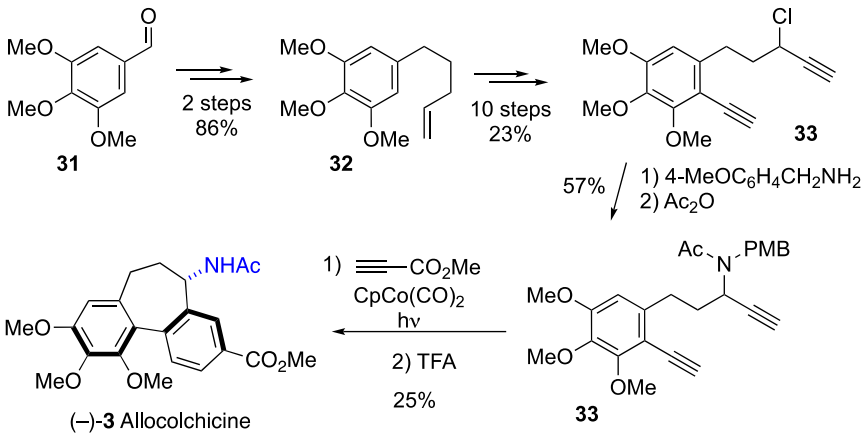
Scheme 5.

Later, Kocienski[16] modified the Astra-Zeneca route by applying Pd-catalysed Suzuki-Miyaura coupling to construct ring B instead of the Ullmann reaction (Scheme 6). In this method, protection of the ketone was not required. The same tropone intermediate **26** was by a simple aldol reaction. To complete the synthesis of *N*-acetylcolchinol (–)-**4** (98% ee), the sequence described by Wulff was employed (Scheme 3).[13] Compared to the Astra-Zeneca route (Scheme 5), the overall yield dropped to 22% due to the increased number of steps.



Scheme 6.

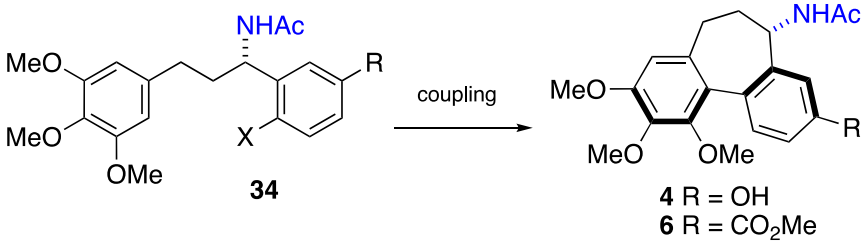
A different approach to the construction of the tricyclic allocolchinoid core was demonstrated by Ramana[17] who synthesised racemic allocolchicine **3** using a Co-catalyzed alkyne [2+2+2]-cyclotrimerisation. First, alkene **32** was synthesised from the commercially available 3,4,5-trimethoxylbenzaldehyde **31** by Grignard addition and deoxygenation. The diyne **33** was achieved in a further 10 steps with a 23% overall yield. Then, the nucleophilic substitution of chloride with *p*-methoxylbenzyl amine followed by acetylation afforded diyne **34**. Finally, the construction of allocolchine **3** was accomplished by the cyclotrimeraization of diyne **34** with methyl propiolate catalysed by $CpCo(CO)_2$ (20 *mol%*) under UV irradiation, followed by deprotection of the PMB group with TFA to furnish (±)-**3** with a 25% yield (Scheme 7).



Scheme 7.

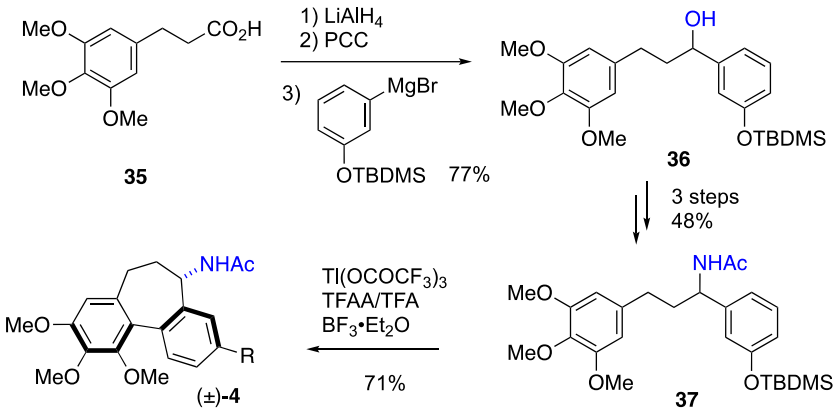
3. Synthetic strategies based on the construction of ring B by arene-arene coupling

Among the plethora of synthetic approaches toward the structural core of the colchicine alkaloids, the routes involving coupling of the two aromatic fragments look most advantageous (Scheme 8), especially considering that the immediate precursors 34 can be prepared by trivial synthetic methods from the readily available materials.



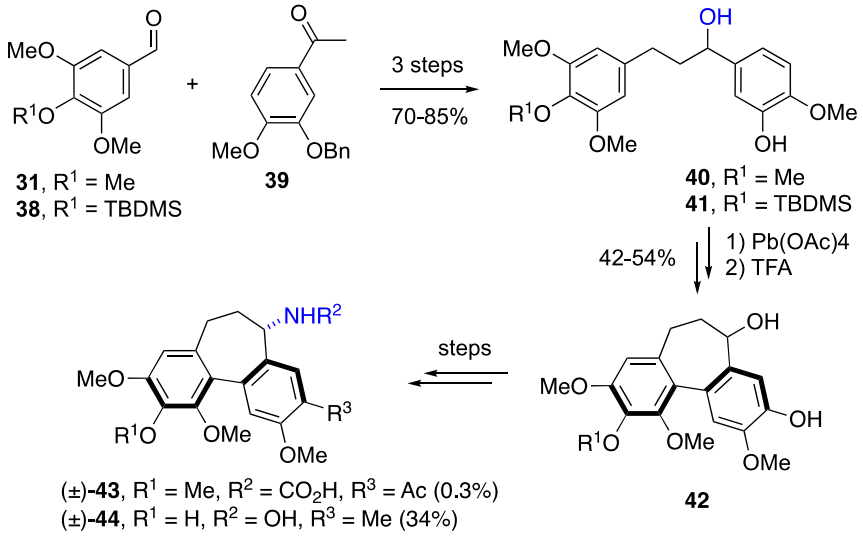
Scheme 8.

The first such method was reported by Macdonald and co-workers.[18] The tricyclic core was built through a non-phenolic oxidative coupling (Scheme 9). Acid **35** was converted to the respective aldehyde through the reduction/oxidation sequence followed by the addition of the Grignard reagent to give racemic 1,3-diphenylpropanol **36** with a 77% yield. The latter was converted in three steps to acetamide **37** through benzylic azidation followed by reduction and acetylation in the overall 48% yield. The target racemic *N*-acetylcolchinol **4** was achieved in 71% yield by a non-phenolic oxidative coupling employing stoichiometric thallium(lll) trifluoroacetate and TFA/TFAA in the presence of boron trifluoride etherate (Scheme 9).



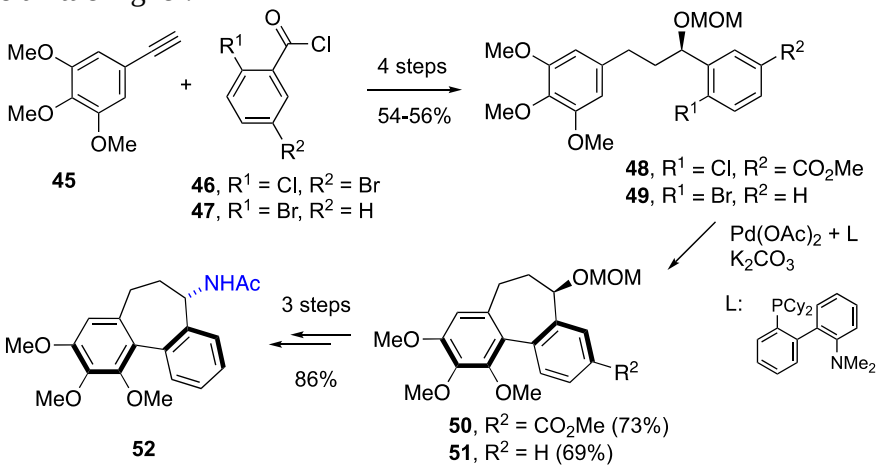
Scheme 9.

This effective synthesis achieved the racemic *N*-acetylcolchinol in 6 steps with a 26% overall yield. However, the major drawback was the use of the toxic Tl^{3+} salt as a stoichiometric oxidant, therefore, new oxidative regents needed to be explored. Banwell and co-workers used a slightly less toxic lead tetraacetate to achieve the arene-arene oxidative coupling for the construction of the seven-membered ring in the synthesis of racemic colchicine and allocolchicinoid analogues **43** and **44** (Scheme 10).[19,20] In their strategy, the synthesis commenced from commercial starting materials **31**/**39** and **38** to afford **40**/**41** in 75-85% yield through the sequence of aldol condensation and reduction. After that, the oxidative cyclisation was carried out with lead tetraacetate and TFA in 42-45% yields. However, the syntheses of racemic **43** and **44** required a further 7 steps which resulted in 0.3% and 34% overall yields, respectively.



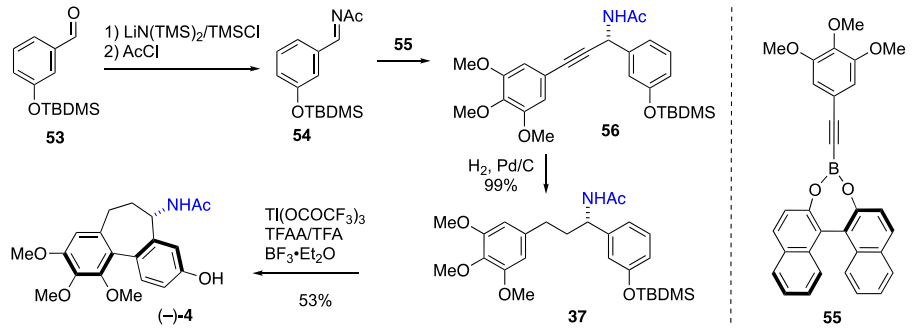
Scheme 10.

The coupling of two aromatic rings can be achieved by employing transition metal catalysis. A total synthesis of allocolchicinoids using palladium catalysis was reported by Fagnou (Scheme 11).[21] It started with joining haloarenes **46** and **47** with alkyne **45** by the Sonogashira cross-coupling, followed by asymmetric reduction of the resulting ketones to the chiral alcohols with (*S*)-pinene/9-BBN in 97% *ee*, which were protected as MOM ethers and then hydrogenated to afford the respective intermediates **48** and **49**. Ring B was constructed by the palladium-catalysed cross-coupling to afford **50** and **51** in 73% and 69% yields. Analogue **52** was synthesized in another three steps from **51**. In this method, the toxic Tl or Pb compounds were not involved in the construction of the seven-membered ring, which is an improvement in terms of the environmental impact, the overall yield was also a little higher.



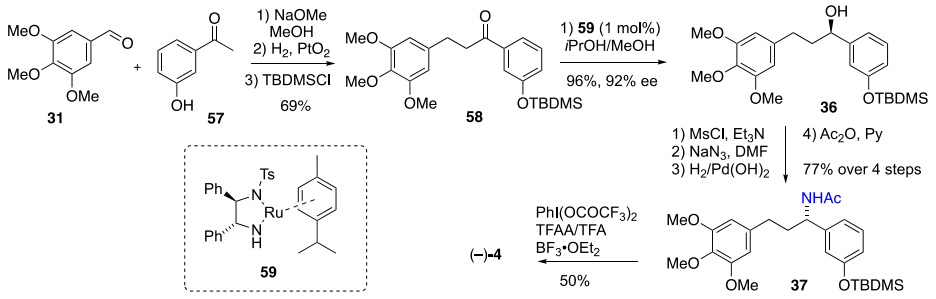
Scheme 11.

A different protocol to install the stereogenic center was proposed by Chong,[22] who employed alkynylation of *N*-acylbenzaldimine **54** with chiral alkynylboronate **55** (Scheme 12). Enantioenriched diarylpropyne **56** was obtained in 72% yield and 94% ee. *N*-acetylaldimine **54** was prepared from aldehyde **53**. Hydrogenation of **56** gave acetamide (–)-**37** which was converted to (–)-*N*-acetylcolchinol **4** following MacDonald's Tl^{3+} oxidative coupling method[18] with a 53% yield (38% overall yield). In this approach, high enantioselectivity and a shorter pathway were achieved.



Scheme 12.

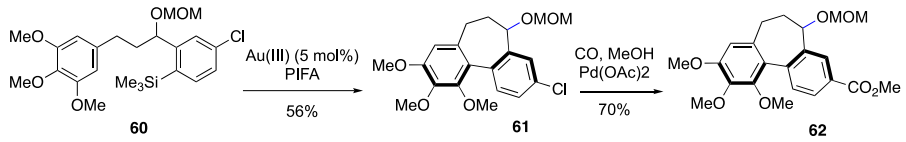
Due to the potential of *N*-acetylcolchinol for pharmaceutical discovery, Kocienski in cooperation with Astra-Zeneca developed several routes amendable to a larger scale.[23] The Sawayer-Macdonald oxidative coupling strategy was adopted but instead of the toxic Tl salts, they introduced non-toxic, readily prepared hypervalent iodine reagents such as iodobenzenediacetate (PIDA) or [bis(trifluoroacetoxy)iodo] benzenes (PIFA). One of the routes is shown in Scheme 13. It started with aldol condensation of commercial reagents **31** and **57** to the respective chalcone, which after hydrogenation and protection of phenol afforded saturated ketone **58**. Asymmetric transfer reduction using catalyst **59** furnished the corresponding chiral alcohol (+)-**36** in 96% yield and 92% ee. After e series of transformation shown in Scheme 13, acetamide (–)-**37** was produced. The target (–)-*N*-acetylcolchinol **4** was accomplished by oxidative intramolecular coupling employing PIFA in 50% yield.



Scheme 13.

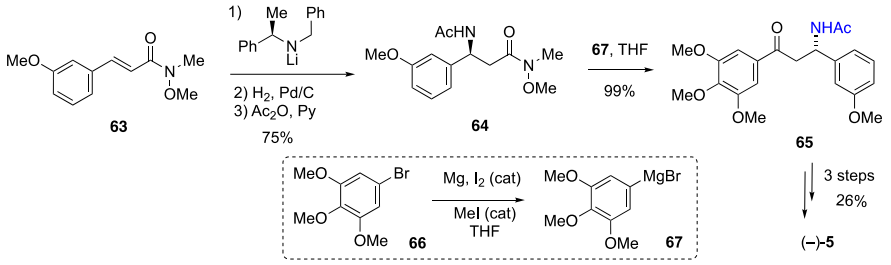
Lloyd-Jones reported a formal total synthesis of racemic allocolchicine **3** via gold-catalysed C-H arylation (Scheme 14).[24] In this strategy, cyclisation of intermediate **60** was achieved by an Au(III)-catalysed coupling to give **61** in 56% yield. The palladium-catalysed carbonylation produced protected

alcohol **62** in 70% yield which can be converted to allocolchicine **3** following the previously described method.[21]



Scheme 14.

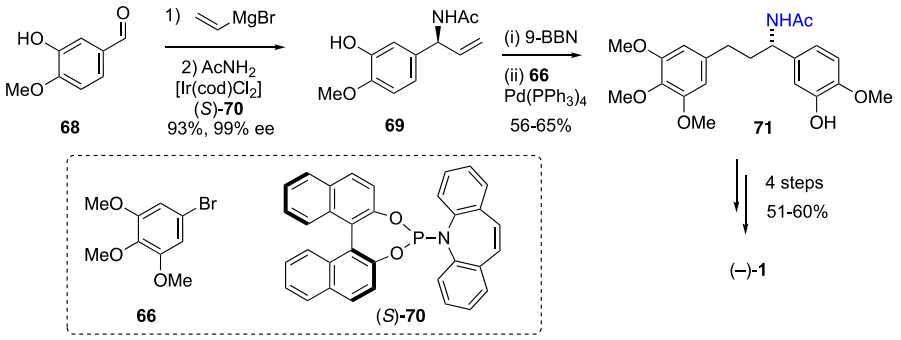
Roberts and co-workers reported an asymmetric synthesis of *N*-acetyl-colchinol methyl ether (–)-**5** (Scheme 15) from α, β-unsaturated Weinreb amide **63** that, in turn, was prepared from the respective commercial aldehyde by Wittig alkenylation.[25] It was then reacted with lithium *N*-benzyl-*N*-(α-methylbenzyl)amide followed by hydrogenolysis and acylation to afford the corresponding enantiopure β-amino amide **64**. The addition of Grignard reagent **67** synthesised in situ from bromide **66** furnished intermediate **65** Further reaction sequence involved the reduction of the ketone, deoxygenation of the alcohol and oxidative arene-arene coupling with PIFA to afford the target (–)-**5**; the overall yield over the final three steps was 26%, where the coupling was the lowest yielding step (30%).



Scheme 15.

In 2021, Yang and co-workers reported a short total asymmetric synthesis of (-)-colchicine **1** in only 7 steps with an overall yield of 27-36%, depending on the scale of the reactions (Scheme 16).[26] In their protocol, the biaryl intermediate **71** was constructed in three steps from the commercial inexpensive isovanillin **68** through vinyl Grignard addition to give the respective racemic alcohol followed by the Ir-catalysed allylic amination in the presence of chiral ligand (*S*)-**70** to furnish chiral acetamide **69** in 93% yield and 99% ee; the reaction was amendable to scaling up without any detrimental effect on the yield or enantioselectivity. The hydroboration of the allylic acetamide **69** with 9-BBN followed by the Pd-catalysed Suzuki coupling with aryl bromide **66** furnished acetamide **71** with yields ranging

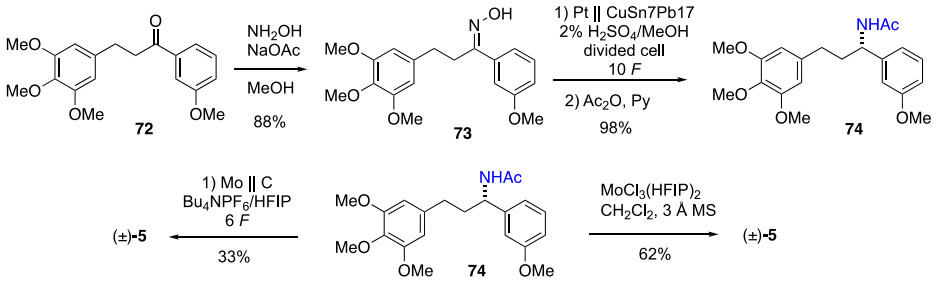
from 56-65%. Finally, treatment of **71** with PIDA and $BF_3 \cdot Et_2O$ gave the cyclised intermediate that in further 3 steps was converted to colchicine (–)-**1** in 51-60% yield over the final 4 steps**.**



Scheme 16.

The reinvigorated interest in electrochemical methodology for organic synthesis,[27–31] prompted the design of the synthetic sequences that employ electrochemistry. Waldvogel and co-workers in their synthesis of *N*-acetylcolchinol methyl ether (±)-**5** attempted to conduct some steps electrochemically (Scheme 17).[32] Thus, cathodic reduction of oxime **73** obtained from the known ketone **72** was accomplished in a nearly quantitative yield using Pt anode and leaded bronze cathode in a divided cell.

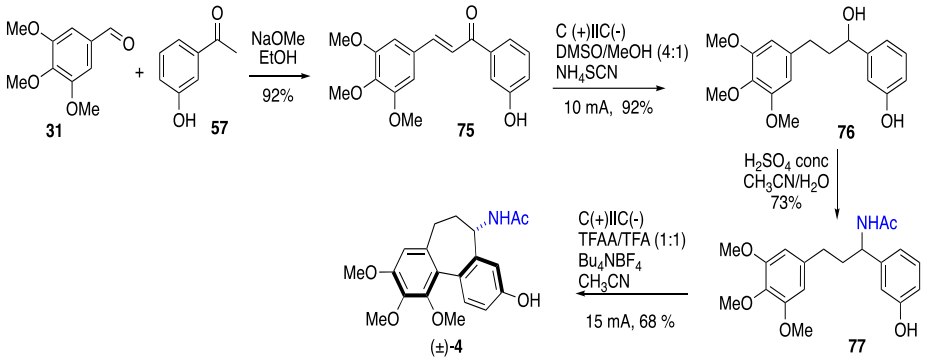
In contrast, optimisation of the electrochemical dehydrogenative coupling of **74** met with limited success. The best yield of **5** (33%) was achieved with Mo anode and carbon graphite cathode in hexafluoroisopropanol (HFIP) in an undivided cell. However, the yield of **5** was improved to 62% through a reagent-mediated coupling using 3 equiv. of $MoCl_3(HFIP)_2$.



Scheme 17.

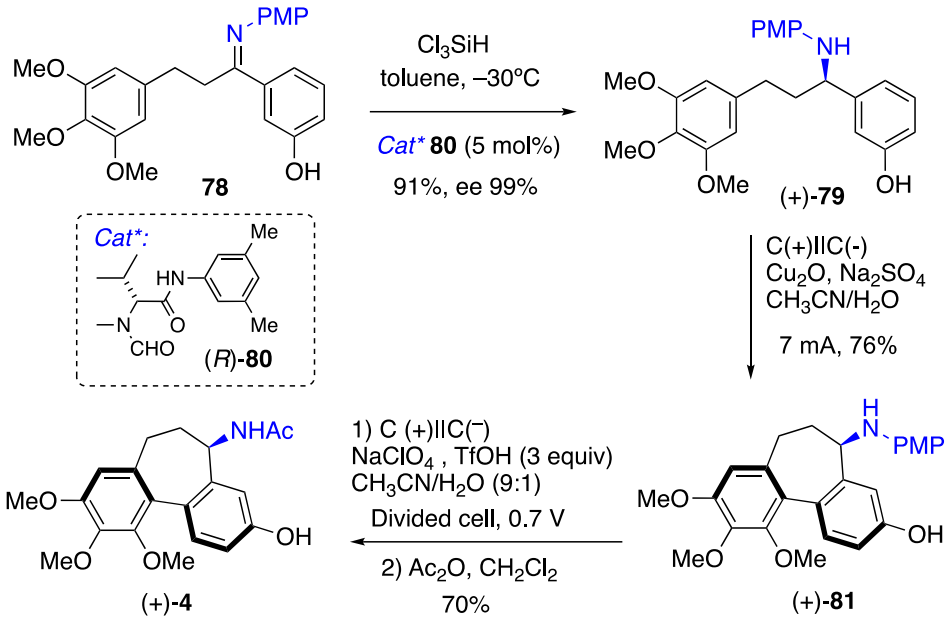
With some experience in this field of electrochemistry,[33–35] Malkov and co-workers[36] designed a short synthetic sequence for *N*-acetylcolchinol **4**, where two out of four steps were carried out electrochemically (Scheme 18). The aldol condensation of the inexpensive, commercially available ace-

tophenone **57** and aldehyde **31** gave chalcone **75** in 92% yield on a 10 mmol scale. Chemoselective cathodic reduction of both the double bond and the carbonyl produced alcohol **76** (92%). Next, the Ritter reaction in aqueous acetonitrile in the presence of concentrated sulfuric acid gave rise to acetamide **77**. In the final step, intramolecular coupling of the two arene rings was accomplished in a 68% yield in a non-divided cell equipped with two carbon electrodes in MeCN in the presence of TFFA and TFA. The entire 4-step synthesis furnished racemic colchinol (±)-**4** in the overall yield of 41% as a single diastereoisomer confirming that the stereoselectivity of the aromatic coupling is controlled by the benzylic stereogenic centre, similar to the oxidative coupling instigated by stoichiometric oxidants.



Scheme 18.

For the enantioselective variant of the synthesis (Scheme 19), 36 imine 78 was obtained from the respective ketone by heating in toluene with p-anisidine in the presence of molecular sieves 5Å. The catalytic asymmetric reduction of 78 with trichlorosilane was carried out in the presence of catalyst 80 to afford a highly enantioenriched amine (+)-79 (91%, 99% ee), which was subjected to electrochemical cyclisation into tricyclic (+)-81 (76%). Finally, electrochemical deprotection of the N-PMP group followed by acylation furnished the target (+)-N-acetylcolchinol 4 in a 70% yield over the two steps. The complete synthetic route from the commercial starting reagents 31 and 57 was accomplished in 7 steps with a 33% over yield.



Scheme 19.

4. Conclusions

In conclusion, the diverse synthetic approaches to colchinoids present a wealth of possibilities for the development of novel compounds with potential therapeutic applications. Earlier methods avoided aromatic coupling and employed starting materials with the pre-existing biaryl fragments, instead focusing on the construction of the 7-membered ring B. As the chemical methodology developed, the synthetic routes relying on cross-coupling came to the forefront of the synthetic endeavours. The methods involved both transition metal-mediated coupling and oxidative coupling of the two aromatic rings using stoichiometric reagents. More recently, electrochemical methodology capable of replacing toxic catalysts or hazardous reagents started to attract the interest of researchers with several novel, more sustainable approaches reported. By considering the strengths and limitations of each method, researchers can strategically navigate the intricacies of the synthesis of colchicine analogues. Future investigations could focus on optimising existing methodology and techniques, exploring innovative synthetic routes, and evaluating the biological activity of newly developed colchinoid derivatives. These efforts contribute to the ongoing quest for enhanced drug discovery and the advancement of medicinal chemistry in the treatment of various diseases.

ԿՈԼԽԻՑԻՆԻ ՇԱՐՔԻ ԱԼԿԱԼՈԻԴՆԵՐԻ ԱՄԲՈՂՋԱԿԱՆ ՍԻՆԹԵԶ

Ի ԴՈՒ, Ա.Վ. ՄԱԼԿՈՎ

Կոլխիցինը հայտնի փսեւդոալկալոիդ է, որը լայնորեն կիրառվում է բժշկության մեջ մնի շարք հիվանդությունների բուժման համար, այդ թվում՝ հոդատապի, արթրիտի, իմունային հիվանդությունների և այլն: Նա հնարավորություն ունի արգելակելու քաղցկեղային բջիջների աճը, սակայն թունավոր է նաև առողջ բջիջների համար: Դա է պատճառը, որ քիմիաթերապիայում կիրառում են կաթնասունների բջիջների համար պակաս թունավոր դեմեկոլցինը, որում ամինախմբի ացետիլ խումբը փոխարինված է մեթիլ խմբով: Ակնարկում կատարված է կոլխիցինի և տարբեր կոլխինոիդների նոր ածանցյալների նպատակաուղղված սինթեզի եղանակների, այլընտրանքային մոտեցումների խոր վերլուծություն: Այն օգտակար կլինի նմանատիպ կառուցվածք ունեցող միացությունների թերապևտիկ ազդեցությամբ օժտված նյութերի սինթեզի համար:

ПОЛНЫЙ СИНТЕЗ АЛКАЛОИДОВ КОЛХИЦИНА

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Колхицин является хорошо известным псевдоалкалоидом, который широко применяется для лечения подагры, иммуноопосредованных заболеваний и псориатического артрита. Он обладает потенциалом ингибировать рост раковых клеток, но оказался токсичным для нормальных клеток. В химиотерапии используется менее токсичный для клеток млекопитающих демеколцин, в котором ацетильная группа в аминогруппе заменена на метильную. В обзоре осуществлен анализ разнообразных подходов, направленных на синтез колхицина и новых производных колхиноидов, которые могут обладать потенциальным терапевтическим действием.

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