Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2022, **24**, 7220

Short electrochemical asymmetric synthesis of (+)-*N*-acetylcolchinol†

Yi Du,[a] Adelaide Lunga,[a] Aleksandr E. Rubtsov [a,b] and Andrei V. Malkov *[a]

Received 20th June 2022,
Accepted 25th August 2022

DOI: 10.1039/d2gc02321k

rsc.li/greenchem

A short synthesis of *N*-acetylcolchinol using a greener and step-economical pathway is reported where all the redox reactions, except for the asymmetric reduction, were carried out electrochemically, replacing protocols that employ transition metals or stoichiometric hazardous reagents. In a 4-step racemic sequence, chemoselective reduction of chalcone and intramolecular oxidative arene–arene coupling were performed in an electrochemical cell giving the target *N*-acetylcolchinol with an overall 41% yield. In a 7-step asymmetric variant, electrochemistry was also employed for the deprotection of *p*-methoxyphenyl amine. The target compound was obtained with a 33% overall yield and 99.5 : 0.5 er.

Introduction

Colchicine **1** (Fig. 1) is a well-known pseudo-alkaloid that has been widely used to treat gout, immune-mediated diseases, and psoriatic arthritis.[1] It was shown to inhibit leukocyte-endothelial cells and T-cells by binding to intracellular tubulin monomers, which prevents their polymerization.[2] Thus, colchicine has the potential to impair the process of antigen recognition and may 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 on the amino group is replaced with methyl, is used in chemotherapy. More recently, based on its anti-inflammatory properties, colchicine was investigated as a potential treatment for COVID-19 with some positive effects reported.[3] Investigation of colchicine analogues revealed that allocolchicinoids derivatives where the 7-membered tropolone ring was replaced with a benzene ring (Fig. 1, **3**–**6**) showed good biological activity and less toxicity compared to the parent colchicine.[4] *N*-Acetylcolchinol **3** is a known tubulin polymerisation inhibitor. Its water-soluble phosphate ZD6126 (**4**) was developed as the prodrug.[5] The phosphate is converted *in vivo* into the active *N*-acetylcolchinol **3**, which binds to the tubulin cytoskeleton of the endothelial cells in tumour blood vessels. ZD6126 selectively induced tumour vascular damage and tumour necrosis at well-tolerated doses in animal models, but it was found to be toxic, therefore, was discontinued. However, the pronounced biological activity of colchicine alkaloids continues to attract the attention of researchers to this class of compounds, thus maintaining the need for robust methodology to access their synthetic analogues. Herein, we present a simple, short and efficient sequence for the synthesis of *N*-acetylcolchinol **3** taking advantage of electrochemical methods.

In the middle of the 20th century, Rapoport[6,7] and Cook[8] reported the first syntheses of *N*-acetylcolchinol methyl ether **5** where the 7-membered ring of the colchinol framework was constructed by the sequence of transformations involving oxidative scission of the respective phenanthrene derivatives. Wulff and co-workers[9] in their synthesis of allocolchicine **6** designed a strategy that centred on a Diels–Alder cycloaddition

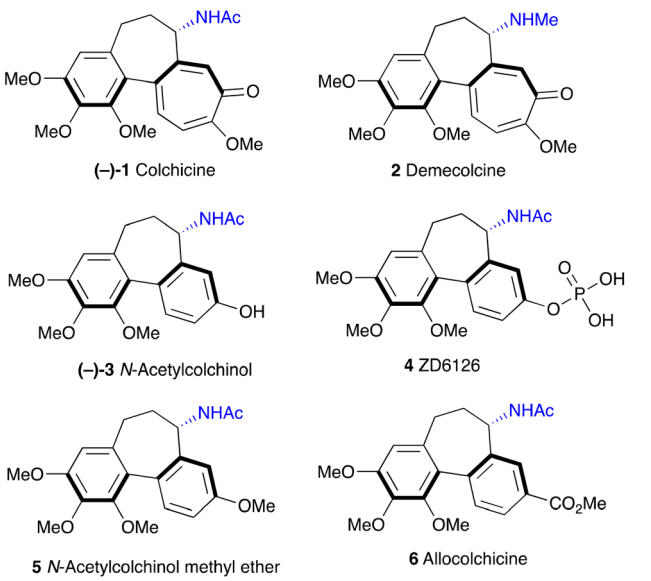
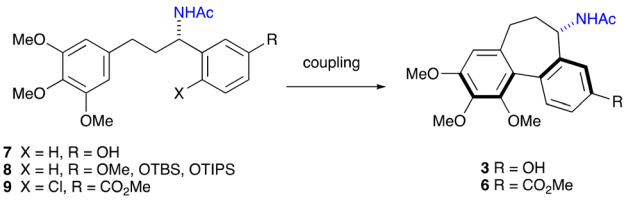


Fig. 1 Colchicine and its analogues.

[a]Department of Chemistry, Loughborough University, Loughborough, LE11 3TU, UK. E-mail: A.Malkov@lboro.ac.uk
[b]Department of Chemistry, Perm State University, Bukireva 15, Perm 614990, Russia

†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2gc02321k



Scheme 1 Cyclisation step in the synthesis of allocolchinoids.

to assemble the methyl benzoate ring of **6**, followed by aromatisation. Since then, a selection of diverse strategies toward colchicine alkaloids were disclosed.[10–15] 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 1),[16–20] especially considering that the immediate precursors **7**–**9** can be prepared by trivial synthetic methods from the readily available materials.

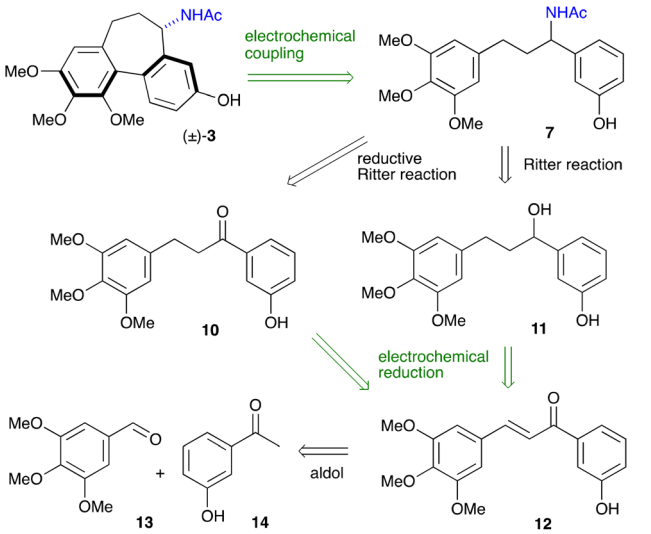
Macdonald[16] reported a non-phenolic intramolecular oxidative coupling of the protected acetamide **8** using stoichiometric quantities of toxic $Tl(O_2CCF_3)_3$. The same protocol was later employed by Chong.[17] Fagnou[18] proposed synthesis of allocolchicine **6** from the intermediate **9** by a Pd(0)-catalysed biaryl coupling, though high catalyst loading (10 mol%) was required. The toxicity of Tl(III) salts prompted a search for safer alternatives. Kocienski[19] synthesised the *N*-acetylcolchinol **3** by intramolecular oxidative coupling of precursor **8** (R = OTBS) using hypervalent iodine(III) reagent $PhI(O_2CCF_3)_2$ (PIFA). More recently, Yang[20] employed $PhI(OAc)_2$ (PIDA) in the oxidative cyclisation step in their gram scale asymmetric synthesis of colchicine **1**. While our manuscript was the preparation, Waldvodgel[21] reported on the electrochemical dehydrogenative coupling of **8** (R = OMe), although in modest yield (33%), which was improved to 62% through a reagent-mediated coupling employing $MoCl_3(HFIP)_2$.

However, the coupling of a simple precursor **7** to **3** remains challenging with the yields generally staying at a modest level. In this report, we present a green and atom-economical synthesis of *N*-acetylcolchinol **3** both in racemic and enantioselective variants, where the redox processes are accomplished electrochemically.

Results and discussion

Racemic synthesis

The reinvigorated interest in electrochemical methodology for organic synthesis,[22–26] and our own recent experience in this field,[27–29] prompted us to design a retrosynthetic sequence for *N*-acetylcolchinol **3**, where two out of four steps are carried out electrochemically (Scheme 2). The first disconnection relies on the C–H/C–H coupling of electron-reach aromatic compound **7**. The acetamide **7** can be obtained either from ketone **10** or from alcohol **11** through the Ritter reaction following the method reported by Doyle.[30] Ketone **10** is included in this retrosynthetic scheme because it enables an enantioselective variant of the synthesis. Based on the previous reports[31,32] and the work from our laboratories,[27–29] we envisaged that both ketone **10** and alcohol **11** can be obtained chemoselectivity by electrochemical reduction of chalcone **12**. The retrosynthetic sequence is completed by the retro aldol disconnection of **12** to the commercially available 3,4,5-trimethoxybenzaldehyde **13** and 3-hydroxyacetophone **14** (Scheme 2).



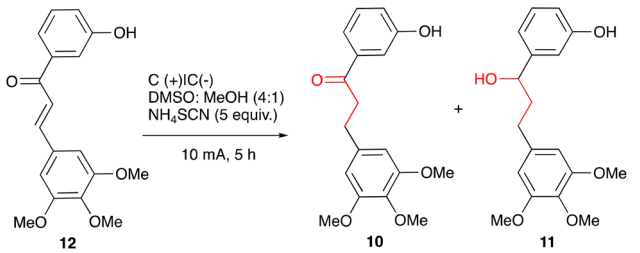
Scheme 2 Proposed retrosynthetic scheme for *N*-acetylcolchinol.

The synthesis commenced with the aldol condensation of the inexpensive, commercially available ketone **14** and aldehyde **13** using ethanolic alkoxide. The resulting chalcone **12** was isolated in 92% yield on a 10 mmol scale; it contains all the carbons of the target molecule skeleton.

Next, attention turned to the reduction of α,β-unsaturated ketone **12** to either ketone **10** or alcohol **11**. Electrochemical reduction of the C–C double bond in unsaturated ketones has been reported recently by us[29] and others,[31,32] though there were no examples of the complete reduction to the saturated alcohol. Mechanistic probes by Xia[31] into the electrochemical hydrogenation of the C–C double bond in chalcones carried out in a 4 : 1 mixture of DMSO/MeOH using Pt plate electrodes and NH_4Cl as an electrolyte revealed that both ammonium cation and methanol can act as proton sources at the cathode whereas DMSO and MeOH[27] are likely to serve as sacrificial reductants at the anode. Therefore, it is reasonable to assume that the double bond is reduced first followed by the reduction of the carbonyl. Taking this into account, we aimed to delineate conditions influencing the relative rates of the two processes.

Some representative optimisation experiments are collected in Table 1. For the full set of the data, see ESI.† First, we focused on the complete reduction of chalcone **12** to alcohol **11**. After some experimentation, it was found that electrolysis of chalcone **12** for 5 hours at RT in a 4 : 1 mixture of DMSO and MeOH containing 5 equiv. of ammonium thiocyanate under the constant current of 10 mA with two carbon plate

Table 1 Optimisation of the reduction of chalcone **12** [a]



Entry	Variation from the standard condition	Yield of **10** [b] (%)	Yield of **11** [b] (%)
1	None	Traces[c]	(92)
2	nBu$_4$NI instead of NH$_4$SCN	52	42
3	nBu$_4$NF instead of NH$_4$SCN	54	40
4	Et$_4$NBF$_4$ instead of NH$_4$SCN	80	12
5	NH$_4$OAc instead of NH$_4$SCN	56	41
6	NH$_4$Cl instead of NH$_4$SCN	60	38
7	DMSO as solvent	60	30
8	MeOH as solvent	NR[d]	NR[d]
9	CH$_3$CN as solvent	95 (92)	Traces[c]
10	DMF as solvent	98	Traces[c]
11	Ni(+)/Ni(−) instead of C(+)/C(−)	89 (82)	Traces[c]
12	C(+)/Ni(−) instead of C(+)/C(−)	50	Traces[c]
13	C(+)/Fe(−) instead of C(+)/C(−)	68	Traces[c]

[a] Reaction conditions: Carbon plate anode, carbon plate cathode, undivided cell; substrate 0.2 mmol, electrolyte 5 equiv. in 10 mL of solvent DMSO/MeOH (4 : 1), constant current (10 mA), reaction time 5 hours. [b] Conversions by LCMS (isolated yields given in parentheses). [c] Detected by LCMS but not isolated. [d] NR = no reaction.

electrodes led selectively to the desired alcohol **11**, which was isolated in a 92% yield; only minor quantities of **10** were detected by LCMS (Table 1, entry 1).

A brief screening of commercially available ammonium salts identified ammonium thiocyanate as optimal for the complete reduction of **12** to **11**. Reduction of ketone **10** to alcohol **11** was distinctly slower when other common electrolytes were employed (Table 1, entries 2–6). Solvent composition proved to be an important factor in achieving high chemoselectivity in the reaction. In pure DMSO, a 2 : 1 mixture of ketone **10** and alcohol **11** was formed, whereas in methanol the reduction was completely suppressed (entries 7 and 8, respectively). The reduction also failed to proceed in DCM. Interestingly, in acetonitrile and DMF, only ketone **10** was obtained, with only traces of the overreduction observed (entries 9 and 10). The same level of selectivity can be attained by employing Ni electrodes instead of carbon (entry 11). A similar effect was achieved by swapping only cathode for Ni or Fe, though at the expense of the overall conversion (entries 11 and 12). In the absence of DMSO and MeOH, only thiocyanate was left to perform the role of the sacrificial reductant,[33] which likely affected the rate of the reduction of **10** to **11**.

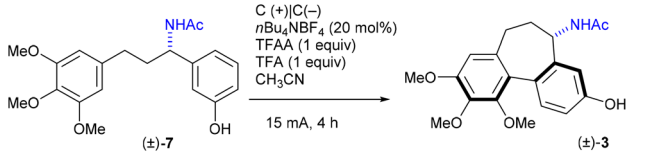
Next, the conversion of alcohol **11** to acetamide **7** was investigated. Doyle and co-workers[30] reported a reductive Ritter reaction where a ketone was treated with triethylsilane in aqueous acetonitrile in the presence of concentrated sulfuric acid to give the respective *N*-acetamide. In this process, the ketone is reduced to the alcohol first, which then undergoes Ritter substitution with acetonitrile. Following this protocol, both ketone **10**, and its mixtures with alcohol **11** (see Table 1), can be converted to acetamide **7** with yields ranging from 56 to 64%. Naturally, pure alcohol **11** does not require the use of triethylsilane. Under the otherwise identical conditions, it was converted to acetamide **7** in a 73% yield.

With acetamide **7** in hand, we embarked on optimising electrochemical conditions for the intramolecular oxidative coupling to furnish the desired colchinol **3** (Table 2). The electrochemical aryl–aryl coupling has been the subject of several investigations in the last two decades,[21,34–38] though the conditions were found to be highly dependent on the nature of the substrates. In the set of electrochemical experiments using racemic **7** to trigger the formation of the 7-membered ring of the target (±)-**3**, the highest yield of 68% has been achieved in a non-divided cell equipped with two carbon electrodes using 10 mol% of nBu$_4$NBF$_4$, in MeCN as the solvent, with 1 equiv. each of TFFA and TFA (Table 2, entry 1). A CV curve for **7** showed one irreversible anodic oxidation peak at 0.45 V *vs.* Ag/AgNO$_3$, whereas product **3** did not contain any redox peaks in the range −0.4 to 0.8 V (see ESI† for details). Other electrolytes showed inferior results (entries 2–5).

According to the previous reports,[34–39] the solvent plays a significant role in the process by stabilising reactive intermediates and tuning nucleophilicity to favour the cross-coupling as opposed to the homo-coupling of two phenols. In our screening experiments, apart from MeCN, only dichloromethane showed some cyclisation, whereas THF and alcohols, including HFIP, appeared to shut down the reaction (entry 6).

At the same time, the addition of a 1 : 1 mixture of TFAA/TFA played an important role as in their absence the yield

Table 2 Optimisation of the oxidative coupling of **7** [a]



Entry	Variation from the standard condition	Yield[b] of **3** (%)
1	None	68
2	nBu$_4$NI instead of nBu$_4$NBF$_4$	Trace
3	nBu$_4$NBr instead of nBu$_4$NBF$_4$	Trace
4	nBu$_4$NHSO$_4$ instead of nBu$_4$NBF$_4$	NR
5	nBu$_4$NF instead of nBu$_4$NBF$_4$	28
6	DCM as solvent[c]	32
7	Without TFAA/TFA	46
8	Without TFAA	22
9	Without TFA	59
10	H$_2$O instead of TFAA/TFA	NR
11	Glassy carbon plate anode and cathode	54

[a] Reaction conditions: Carbon plate anode, carbon plate cathode, undivided cell; substrate 0.1 mmol, 20 mol% electrolyte in 7 mL of solvent, constant current (15 mA), additives 1 equiv. each, reaction time 4 hours. [b] Isolated yield. [c] In other solvents, such as MeOH, iPrOH, THF and HFIP, only product traces were detected by LCMS. HFIP = (CF$_3$)$_2$CHOH.

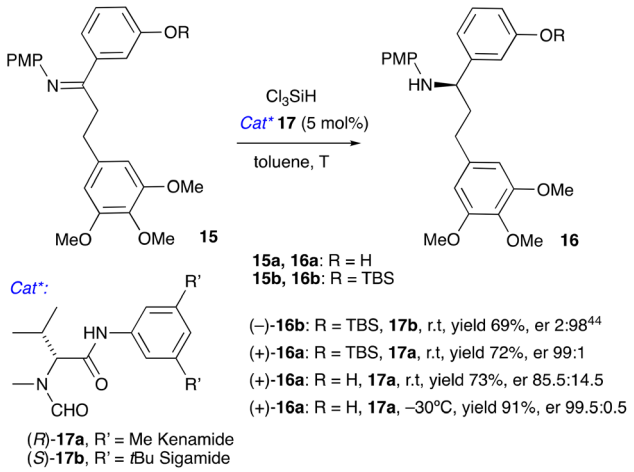
decreased (entries 7–9). No cyclisation took place in the presence of water (entry 10). Glassy carbon electrodes exhibited a slightly lower yield compared to the standard carbon plate electrodes (entry 11).

With the optimised conditions for each step, the overall 4-step synthesis of racemic colchinol **3** is presented in Scheme 3. The target compound (±)-**3** was obtained 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.[19,20,40] Next, the attention turned to the enantioselective variant of the synthesis.

Asymmetric variant

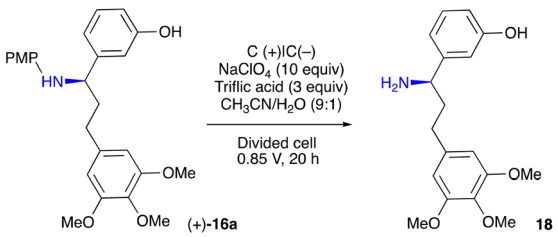
We envisaged that ketone **10** can be converted to imine **15** by condensation with 4-methoxyaniline followed by organocatalytic asymmetric reduction to amine **16** using the method developed in our laboratories.[41–43] Reduction of a TBS-protected imine **15b** with trichlorosilane in the presence of catalyst **17b** was reported by us previously;[40,44] catalyst **17a** synthesised from unnatural D-valine performed equally well (Scheme 4). To avoid the extra silylation step of converting **15a** to **15b**, we investigated the reduction of the unprotected **15a**. At room temperature, the enantioselectivity was modest, but it improved dramatically by lowering the reaction temperature to −30 °C. Amine **16a** was obtained in a 91% yield and 99.5 : 0.5 er. We also attempted this reaction as a one-pot reductive amination,[45,46] but combining prolonged heating required to convert ketone **10** to amine **15a** with a low-temperature reduction proved challenging, therefore we settled for a two-step protocol.

With the enantiopure **16a** in hand, we next turned to electrochemical oxidative removal of the 4-methoxyphenyl group (PMP) in **16a**. Mioskowski and Royer[47] reported electrochemical deprotection of the PMP employing Pt electrodes in a divided cell. However, under their conditions, a low conversion in the formation of **18** was observed (Table 3, entry 5). Additional experiments were carried out to identify the



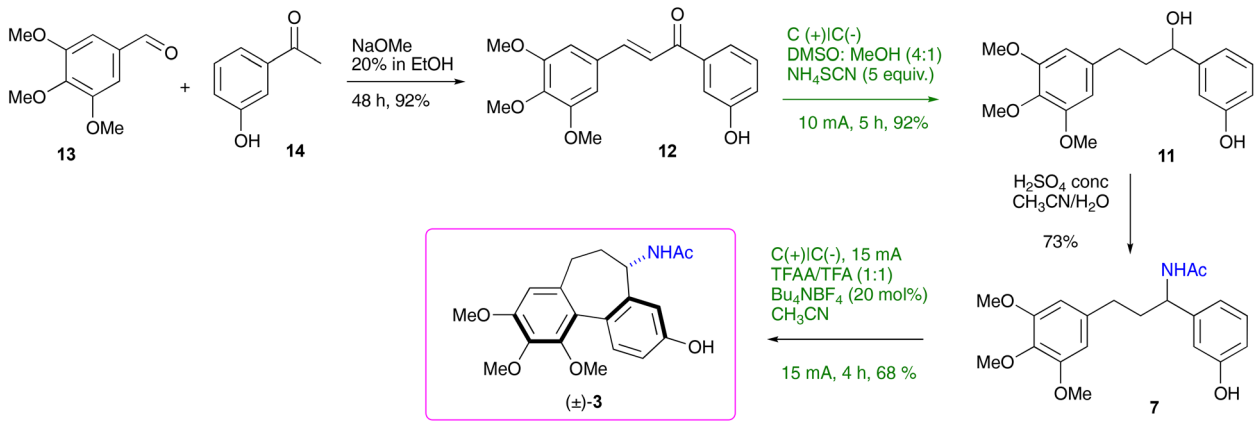
Scheme 4 Asymmetric synthesis of chiral amines **16** and **17**. (PMP = 4-MeOC$_6$H$_4$, TBS = *t*BuMe$_2$Si).

Table 3 Optimisation of the oxidative deprotection of **16a** [a]



Entry	Variation from the standard condition	Yield[b] of **18** (%)
1	None	76 (62[c])
2	TFA instead of triflic acid	Trace
3	H_2SO_4 instead of triflic acid	Trace
4	Without triflic acid or H_2O	Trace
5	Pt(+)/Pt(−) instead of C(+)/C(−)	30

[a] Reaction conditions: Carbon plate anode, carbon plate cathode, divided cell; substrate 0.1 mmol, 10 equiv. of electrolyte in 20 mL of solvent, constant voltage (0.85 V), additive 0.5 equiv., reaction time 20 hours. [b] Conversion by LC-MS. [c] Isolated yield of (+)-7 after the treatment of **18** with acetic anhydride in DCM.



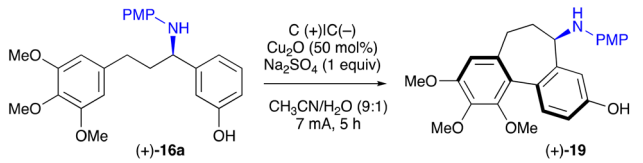
Scheme 3 Synthesis of (±)-*N*-acetylcolchinol.

optimal conditions as follows: amine **16a** (0.1 mmol) was electrolysed under the constant potential of 0.85 V for 20 h at RT in a divided cell equipped with carbon plate electrodes, in a 9 : 1 mixture of MeCN and H_2O (20 mL) containing 10 equiv. of $NaClO_4$ and 3 equiv. of triflic acid. This led to a free amine **18**, which after a standard workup (for details, see ESI†) was acylated to furnish pure (+)-**7** in a 62% yield (Table 3, entry 1).

Triflic acid proved to be an important component of the mixture, as attempts to remove it or replace it with other acids failed to give any product (entries 2–4).

It was noted that among the competing side reactions of the removal of the PMP group in **16a** was its oxidative cyclisation into **19**, which represents an attractive alternative route to the target colchinol (+)-**3**. Therefore, this reaction was investigated next (Table 4).

Table 4 Optimisation of the oxidative coupling of **16a** [a]

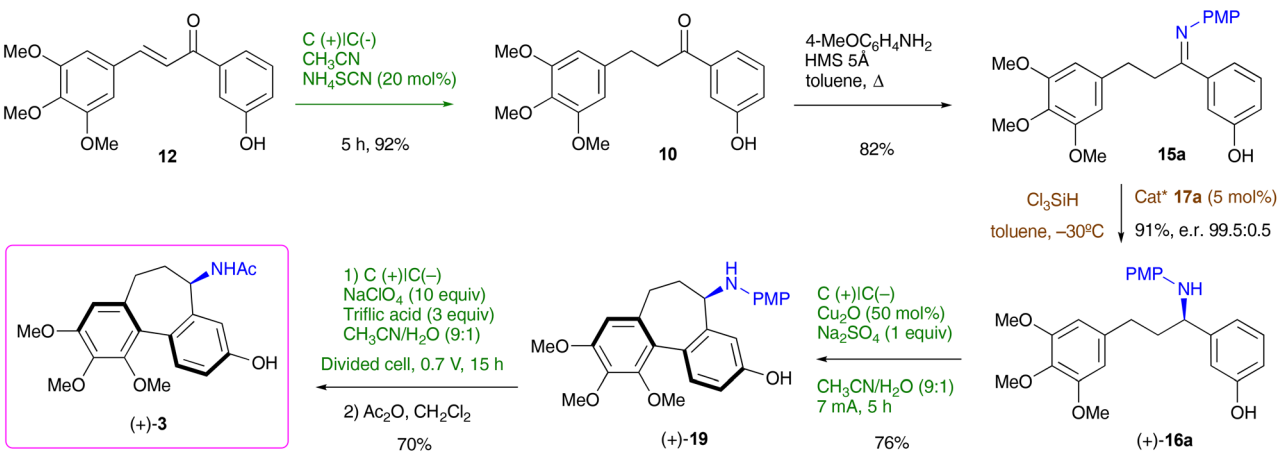


Entry	Variation from the standard condition	Yield[b] of **19** (%)
1	None	82 (74[c])
2	$CuSO_4$ instead of Cu_2O	50
3	CuCl instead of Cu_2O	56
4	CuBr instead of Cu_2O	60
5	$Cu(MeCN)_4BF_4$ instead of Cu_2O	53
6	With triflic acid	70 (56[c])
7	Without H_2O	20
8	K_2SO_4 instead of Na_2SO_4	76 (63[c])
9	Pt(+)/Pt(–) instead of C(+)/C(–)	48
10	Cu(+)/Cu(–) instead of C(+)/C(–)	Trace

[a] Reaction conditions: Carbon plate anode, carbon plate cathode, undivided cell; substrate 0.1 mmol, 20 mol% electrolyte in 7 mL of solvent, constant current (7 mA), additives 1 equiv. each, reaction time 4 hours. [b] Conversion by LC-MS. [c] Isolated yield.

The conditions employed for the cyclisation of acetamide **7** (Table 2) have undergone some modifications. First, it was found that the addition of Cu_2O played a crucial role in promoting oxidative aromatic coupling (Table 4, entry 1). Other Cu(I) and Cu(II) salts also gave the desired product but were slightly less efficient (entries 2–5). The beneficial effect of Cu is not surprising as for a long time Cu salts have been used, both stoichiometrically and catalytically, to effect biaryl cross-coupling.[48,49] Switching to an aqueous solvent was another important change to the original protocol as a poor conversion was observed in anhydrous acetonitrile (entry 7). At the same time, the addition of acid was found no longer necessary (entry 6). In the aqueous reaction medium, simple inorganic salt can be used as supporting electrolytes (entries 1 and 8). The reaction is best carried out in an undivided cell equipped with carbon plate electrodes. Using other electrode materials gave inferior results (entries 9 and 10). It is worth noting that when the optimal conditions for the oxidative coupling of **16a** were applied to acetamide **7**, low conversion was observed (see ESI, Table S2†), suggesting that the substituents on the nitrogen play a significant role.

For the overall enantioselective synthesis of (+)-*N*-acetylcolchinol **3** we opted for the route involving cyclisation of (+)-**16a** into (+)-**19**. The synthetic sequence that commences with the unsaturated ketone **12** is presented in Scheme 5. Chemoselective electrochemical hydrogenation of **12** (Table 1, entries 9 and 10) furnished ketone **10** in 92% yield, which was converted to imine **15a** (82%) by heating in toluene with 4-methoxyaniline in the presence of molecular sieves 5Å. Catalytic asymmetric reduction of **15a** with trichlorosilane in the presence of **17a** gave rise to a highly enantioenriched amine (+)-**16a** (91%, er 99.5 : 0.5), which was subjected to electrochemical cyclisation (Table 4, entry 1) to afford tricyclic (+)-**19** (76%). Finally, electrochemical deprotection of the *N*-PMP group (a slightly lower voltage and a shorter time were used compared to those shown in Table 3) followed by acylation furnished the target (+)-*N*-acetylcolchinol **3** in a 70% yield over the two steps. The complete synthetic route from the com-



Scheme 5 Synthesis of (+)-*N*-acetylcolchinol **3**.

mercial starting reagents **13** and **14** was accomplished in 7 steps with a 33% overall yield.

Conclusions

In summary, we have developed two variants of stereoselective synthesis of *N*-acetylcolchinol where the reagent-based redox steps were replaced with mild electrochemical protocols. In a 4-step racemic variant, we first developed an efficient electrochemical procedure for the reduction of α,β-unsaturated ketone chemoselectively either to saturated alcohol or ketone. Then, the electrochemical conditions were optimised to achieve phenolic oxidative cyclisation of *N*-acetamide into *N*-acetylcolchinol. In the entire sequence, all the reactions were completed at room temperature with an overall yield of 41%.

In a 7-step enantioselective version, the saturated ketone was converted to the imine by the reaction with 4-methoxyaniline. The imine was reduced to the respective enantioenriched amine by organocatalytic reduction with trichlorosilane with er 99.5 : 0.5. The next two redox steps, oxidative phenolic coupling and removal of the *N*-PMP group, were carried out electrochemically followed by acylation of the free amine to furnish the dextrorotatory enantiomer of *N*-acetylcolchinol in a 33% overall yield. Overall, this work showcases the enabling power of electrochemical redox methods in application to the stereoselective synthesis of complex molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

YD and AVM thank H2020 BBI JU for the PHENOLEXA Grant 101023225. RAE thanks the Russian Science Foundation for Grant 18-73-10156. YD and AL acknowledge additional support from Loughborough University.

References

1 P. G. Shekelle, S. J. Newberry, J. D. FitzGerald, A. Motala, C. E. O'Hanlon, A. Tariq, A. Okunogbe, D. Han and R. Shanman, *Ann. Intern. Med.*, 2017, **166**, 37–51.
2 G. Taraboletti, G. Micheletti, R. Dossi, P. Borsotti, M. Martinelli, F. Fiordaliso, A. J. Ryan and R. Giavazzi, *Clin. Cancer Res.*, 2005, **11**, 2720–2726.
3 A. Z. Reyes, K. A. Hu, J. Teperman, T. L. Wampler Muskardin, J.-C. Tardif, B. Shah and M. H. Pillinger, *Ann. Rheum. Dis.*, 2021, **80**, 550–557.
4 A. Brossi, *J. Med. Chem.*, 1990, **33**, 2311–2319.
5 P. M. LoRusso, S. M. Gadgeel, A. Wozniak, A. J. Barge, H. K. Jones, Z. S. DelProposto, P. A. DeLuca, J. L. Evelhoch, S. A. Boerner and C. Wheeler, *Invest. New Drugs*, 2008, **26**, 159–167.
6 H. Rapoport, A. R. Williams and M. E. Cisney, *J. Am. Chem. Soc.*, 1950, **72**, 3324–3325.
7 H. Rapoport, A. R. Williams and M. E. Cisney, *J. Am. Chem. Soc.*, 1951, **73**, 1414–1421.
8 J. Cook, J. Jack, J. Loudon, G. Buchanan and J. MacMillan, *J. Chem. Soc.*, 1951, 1397–1403.
9 A. V. Vorogushin, A. V. Predeus, W. D. Wulff and H.-J. Hansen, *J. Org. Chem.*, 2003, **68**, 5826–5831.
10 T. Graening and H. G. Schmalz, *Angew. Chem., Int. Ed.*, 2004, **43**, 3230–3256.
11 M. G. Banwell, J. N. Lambert, M. F. Mackay and R. J. Greenwood, *J. Chem. Soc., Chem. Commun.*, 1992, 974–975.
12 M. G. Banwell, M.-A. Fam, R. W. Gable and E. Hamel, *J. Chem. Soc., Chem. Commun.*, 1994, 2647–2649.
13 S. Djurdjevic and J. R. Green, *Org. Lett.*, 2007, **9**, 5505–5508.
14 S. D. Broady, M. D. Golden, J. Leonard, J. C. Muir and M. Maudet, *Tetrahedron Lett.*, 2007, **48**, 4627–4630.
15 G. Besong, D. Billen, I. Dager, P. Kocienski, E. Sliwinski, L. R. Tai and F. T. Boyle, *Tetrahedron*, 2008, **64**, 4700–4710.
16 J. S. Sawyer and T. L. Macdonald, *Tetrahedron Lett.*, 1988, **29**, 4839–4842.
17 T. R. Wu and J. M. Chong, *Org. Lett.*, 2006, **8**, 15–18.
18 M. Leblanc and K. Fagnou, *Org. Lett.*, 2005, **7**, 2849–2852.
19 G. Besong, K. Jarowicki, P. J. Kocienski, E. Sliwinski and F. T. Boyle, *Org. Biomol. Chem.*, 2006, **4**, 2193–2207.
20 X. Liang, L. Li, K. Wei and Y.-R. Yang, *Org. Lett.*, 2021, **23**, 2731–2735.
21 D. Pollok, F. U. Rausch, S. B. Beil, P. Franzmann and S. R. Waldvogel, *Org. Lett.*, 2022, **24**, 3760–3765.
22 B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099–2119.
23 M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230–13319.
24 A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594–5619.
25 S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 6018–6041.
26 M. C. Leech, A. D. Garcia, A. Petti, A. P. Dobbs and K. Lam, *React. Chem. Eng.*, 2020, **5**, 977–990.
27 A. Alkayal, V. Tabas, S. Montanaro, I. A. Wright, A. V. Malkov and B. R. Buckley, *J. Am. Chem. Soc.*, 2020, **142**, 1780–1785.
28 A. M. Sheta, M. A. Mashaly, S. B. Said, S. S. Elmorsy, A. V. Malkov and B. R. Buckley, *Chem. Sci.*, 2020, **11**, 9109–9114.
29 A. M. Sheta, A. Alkayal, M. A. Mashaly, S. B. Said, S. S. Elmorsy, A. V. Malkov and B. R. Buckley, *Angew. Chem., Int. Ed.*, 2021, **60**, 21832–21837.

30 M. P. Doyle, D. J. DeBruyn, S. J. Donnelly, D. A. Kooistra, A. A. Odubela, C. T. West and S. M. Zonnebelt, *J. Org. Chem.*, 1974, **39**, 2740–2747.
31 B. Huang, Y. Li, C. Yang and W. Xia, *Chem. Commun.*, 2019, **55**, 6731–6734.
32 Y. Qin, J. Lu, Z. Zou, H. Hong, Y. Li, Y. Li, L. Chen, J. Hu and Y. Huang, *Org. Chem. Front.*, 2020, **7**, 1817–1822.
33 V. A. Kokorekin, V. L. Sigacheva and V. A. Petrosyan, *Tetrahedron Lett.*, 2014, **55**, 4306–4309.
34 J. L. Röckl, D. Pollok, R. Franke and S. R. Waldvogel, *Acc. Chem. Res.*, 2020, **53**, 45–61.
35 S. R. Waldvogel, S. Lips, M. Selt, B. Riehl and C. J. Kampf, *Chem. Rev.*, 2018, **118**, 6706–6765.
36 K. Okamoto and K. Chiba, *Org. Lett.*, 2020, **22**, 3613–3617.
37 A. Lipp, M. Selt, D. Ferenc, D. Schollmeyer, S. R. Waldvogel and T. Opatz, *Org. Lett.*, 2019, **21**, 1828–1831.
38 A. Lipp, D. Ferenc, C. Gütz, M. Geffe, N. Vierengel, D. Schollmeyer, H. J. Schäfer, S. R. Waldvogel and T. Opatz, *Angew. Chem., Int. Ed.*, 2018, **57**, 11055–11059.
39 A. Kirste, M. Nieger, I. M. Malkowsky, F. Stecker, A. Fischer and S. R. Waldvogel, *Chem. – Eur. J.*, 2009, **15**, 2273–2277.
40 A. V. Malkov and P. Kočovský, in *Lewis Base Catalysis in Organic Synthesis*, ed. E. Vedejs and S. E. Denmark, Wiley-VCH Verlag GmbH & Co, Weinheim, Germany, 2016, vol. 3, ch. 20, pp. 1011–1038.
41 A. V. Malkov, A. Mariani, K. N. MacDougall and P. Kočovský, *Org. Lett.*, 2004, **6**, 2253–2256.
42 A. V. Malkov, S. Stončius, K. N. MacDougall, A. Mariani, G. D. McGeoch and P. Kočovský, *Tetrahedron*, 2006, **62**, 264–284.
43 A. V. Malkov, K. Vrankova, R. C. Sigerson, S. Stončius and P. Kočovský, *Tetrahedron*, 2009, **65**, 9481–9486.
44 A. V. Malkov, K. Vrankova, S. Stoncius and P. Kocovsky, *J. Org. Chem.*, 2009, **74**, 5839–5849.
45 A. V. Malkov, S. Stončius and P. Kočovský, *Angew. Chem., Int. Ed.*, 2007, **46**, 3722–3724.
46 K. K. Popov, J. L. P. Campbell, O. Kysilka, J. Hošek, C. D. Davies, M. Pour and P. Kočovský, *J. Org. Chem.*, 2022, **87**, 920–943.
47 S. De Lamo Marin, T. Martens, C. Mioskowski and J. Royer, *J. Org. Chem.*, 2005, **70**, 10592–10595.
48 P. Kočovský, Š. Vyskočil and M. Smrčina, *Chem. Rev.*, 2003, **103**, 3213–3246.
49 Y. E. Lee, T. Cao, C. Torruellas and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2014, **136**, 6782–6785.