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Gram-Scale, Seven-Step Total Synthesis of (−)-Colchicine

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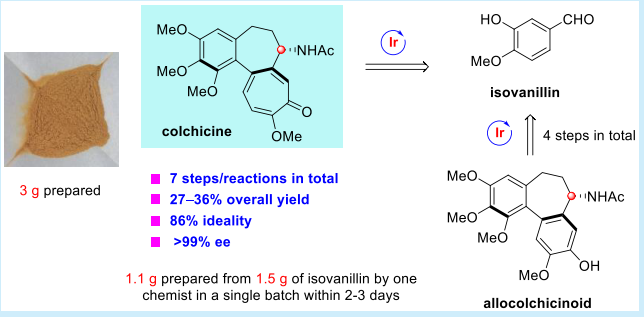
ABSTRACT: Herein we report a streamlined, gram-scale total synthesis of (−)-colchicine that takes only 7 easy steps, with an overall yield of 27−36%. To warrant the synthetic efficiency and practicality of (−)-colchicine, we tactically utilized a modified version of a powerful Ir-catalyzed amidation reported by Carreira to install the key chiral C-7 acetamido group, Suzuki and biomimetic phenol oxidative coupling, and Banwell-inspired cyclopropane ring cleavage to construct (−)-colchicine precisely and rapidly. Remarkably, a described strategy also can shorten the synthesis of allocolchicinoid to 4 steps.



Colchicine (**1**), one of the major alkaloid constituents of the autumn crocus, is a well-known drug used for the treatment of gout and familial Mediterranean fever.[1] While colchicine is not clinically approved for cancer treatment due to toxicity, it exerts remarkable antimitotic activity induced by interaction with tubulin, for which it can still be used as a lead compound for the generation of potential anticancer drugs. In recent years, numerous analogues of colchicine have been synthesized in the hope of developing less toxic anticancer drugs.[2] Given that the published synthetic routes to colchicine are lengthy and far from ideal, using the natural colchicine as a starting material is the regular or only means of acquiring the colchicine-based derivatives. In this way, the problems of how to achieve sustainable and reliable access to natural isolate and diminish the ecological impact could not be ignored if a promising anticancer drug is discovered and the ensuing commercial production is essential. Furthermore, unlike total synthesis, which has a powerful flexibility in making molecules, semisynthesis based on natural colchicine has its limitations when a greater analog diversity is needed.

Allocolchicinoids (**2**−**5**), a new type of synthetic derivatives of colchicine in which the tropolone ring is replaced by a benzene ring, have promising anticancer bioactivities but with reduced toxicity (Figure 1).[3] Of note, ZD6126 (**5**), developed by AstraZeneca,[4] is a novel vascular-targeting agent that causes selective destruction of tumor vasculature. Although they are void of the exotic tropolone nucleus, allocolchicinoids still pose a surprisingly great synthetic obstacle in previous synthetic routes that normally require 10−20 steps.[3] Taken together, despite being deceptively straightforward in the structures, colchicine (**1**) and allocolchicinoids are synthetic challenging targets; especially for colchicine (**1**) much attention has been oriented to its total synthesis in recent decades. Although several elegant routes have emerged,[5] there was no genuinely practical synthesis of **1** for the past 60 years.[5a]

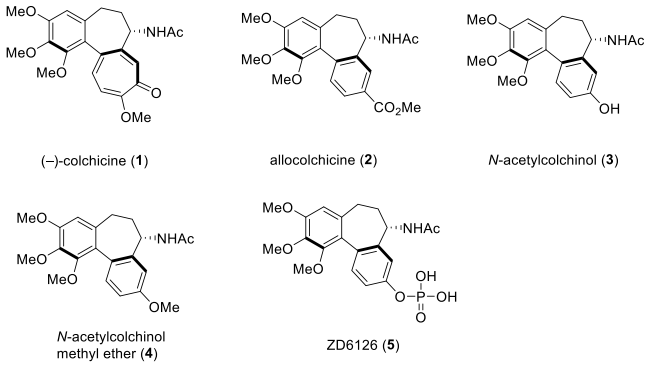


Figure 1. Structures of colchicine (**1**) and representative allocolchicinoids **2**−**5**. .

In the first synthesis reported by Eschenmoser[5b] and Schreiber in 1959, two key problems associated with colchicine synthesis were disclosed, which to date still have not been completely and simultaneously resolved. The first issue is site-selective and stereoselective introduction of the C-7 acetamido group in **1**, although solutions have been advanced by Nakamura,[5c] Woodward,[5d] Evans,[5e] Banwell,[5f,g] Cha,[5h,i] Schmalz,[5j,k] and Li.[5l,m] The second issue is regiocontrolled synthesis of the tropolone nucleus. For this issue, before Banwell's work, 10-demethylcolchicine was used as a final intermediate, which experiences tautomerism that results in a

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mixture of colchicine (**1**) and isocolchicine.[5a,o] In 1996, Banwell reported an elegant solution of biomimetic ring expansion of cyclopropane to generate the tropolone nucleus in **1** (Figure 2).[5g] Later, Cha,[5h,i] Schmalz,[5j,k] and Li[5l,m] adopted

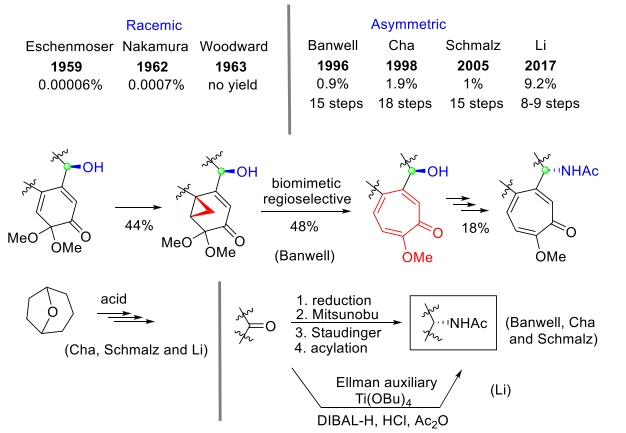

Figure 2. A synopsis of the previous syntheses of colchicine.

an alternative strategy based on a ring opening reaction of an oxa bridge intermediate, prepared through cycloaddition from a furan or a carbonyl ylide. Unlike Banwell's solution, the latter strategy could not provide the tropolone ring immediately and required additional steps. Despite those advances, efficiently addressing the above two problems simultaneously remains a challenging goal, as demonstrated by the extremely low yielding syntheses in earlier studies and poor yielding syntheses of 1996−2005 (Figure 2). Notably, at the beginning of our synthesis, Li and co-workers reported an elegant synthesis of colchicine (**1**) that needed 8 or 9 steps with an improved overall yield.[5l,m] After careful examination, we found there were approximately 15 reactions in Li's route. It was the execution of several one-pot reactions that contributed remarkably to the step economy.[6] Although a one-pot reaction can be counted as one step, time economy and the use of multiple concession reactions are still far from ideal.[6,7] For instance, while addressing the first issue, Li used a process consisting of Ellman auxiliary addition to a ketone group, reduction of the imine, removal of the auxiliary, and acetylation (Figure 2). As previously mentioned, the first issue of colchicine's C-7 acetamido group installation is a longstanding conundrum. In other syntheses described by Banwell,[5f,g] Cha,[5h,i] and Schmalz,[5k] they unanimously used similar strategies in which four concession steps were required: asymmetric reduction of a ketone, Mitsunobu inversion with an azide, Staudinger reaction, and acylation. To solve this problem, one-step, direct transformation would be "ideal".

Before discussing our chemical synthesis of colchicine (**1**), it is worth illustrating the pathway established for the biosynthesis of colchicine.[8] Having emerged in the 1960s, and reported as late as 2020, a near-complete biosynthetic pathway has been elucidated. As shown in Figure 3, a series of methylations and phenyl ring hydroxylation of Pictet−Spengler product **6** generate autumnaline (**7**), upon which a critical oxidative para−para phenol coupling occurs and then a methylation affords *O*-methylandrocymbine (**8**). Next, another crucial transformation, namely, formation of the characteristic tropolone ring has proven to be a cyclopropane ring cleavage process catalyzed by a noncanonical cytochrome P450 (**9** → **10** → **11**). Based on the proposed pathway for colchicine biosynthesis, as discussed in the preceding paragraph, in 1996, Banwell reported an elegant biomimetic strategy in which the tropolone ring was brilliantly constructed through a cyclopropane ring cleavage process. However, the efficiency of the biomimetic synthesis was significantly decreased by a series of low yielding transformations (Figure 2), largely because of their inability to satisfactorily solve the first issue of colchicine chemical synthesis as we noted earlier. We hypothesized that the use of a free hydroxyl group might be the real culprit eroding Banwell's creative design, leading to a 0.9% overall yield. By contrast, if the more stable, chiral acetamido group was used directly, the scenario would be fundamentally changed not only because the natural product would be obtained asymmetrically after a rearrangement but also because the low yielding issue encountered in the case of the free hydroxyl group could be avoided. Taking account of the unparalleled conciseness but with apparent limitation of Banwell's cyclopropane rearrangement in the biomimetic synthesis for colchicine (**1**), we decided to revisit a similar strategy at the final stage that ultimately would bring about an "ideal" chemical synthesis competing with the biosynthesis in terms of efficacy.

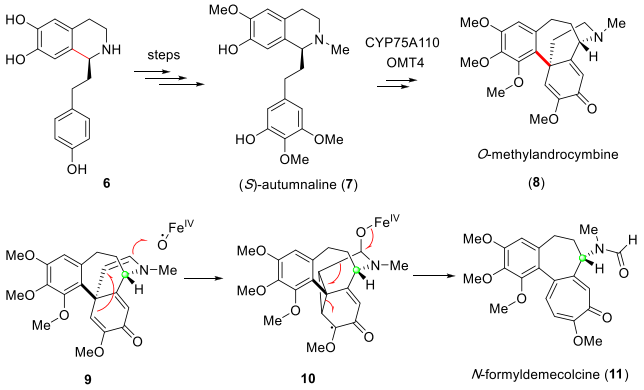

Figure 3. A brief description of the biosynthesis of colchicine.

A robust synthesis of colchicine (**1**) demands inexpensive chemical inputs, step economy, time economy, and overall efficiency. As shown in Scheme 1, inexpensive isovanillin (**12**) was selected as the starting material. Rapid addition of vinyl Grignard reagent to isovanillin provided a quantitative yield of a secondary allylic alcohol **13** in 10 min, thereby setting the stage to install the C-7 acetamido group. Initially, we followed Carreira's protocol,[9a] using sulfamic acid[9b,c] as the ammonia equivalent, and the capture of a chiral primary amine intermediate with acetyl chloride was carried out in a one-pot reaction. Despite our efforts, the reaction of our substrate **13** gave an unsatisfactory yield (<35%) of allylic acetamide **14** with approximately 90% ee. We observed that the phenolic hydroxyl group of **13** could be involved in the acetylation, which complicated the reaction. To exclude a protecting group for the free phenol, we hypothesized that the direct use of acetamide as a nucleophile would be possible in this key step. After extensive studies (see the Supporting Information (SI)), we found that by using 0.2 equiv of $BF_3{\cdot}Et_2O$ as a promoter, 1,4-dioxane (0.5 M) as the solvent, and $[\{Ir(cod)Cl\}_2]$/(*S*)-**L** as the catalyst,[10] the proposed direct substitution of racemic hydroxyl with acetamide afforded allylic acetamide **14** in 93% yield with >99% ee in 1 h. Gratifyingly, the yield and ee of the reaction seemed unaffected during scale-up. Moreover, we

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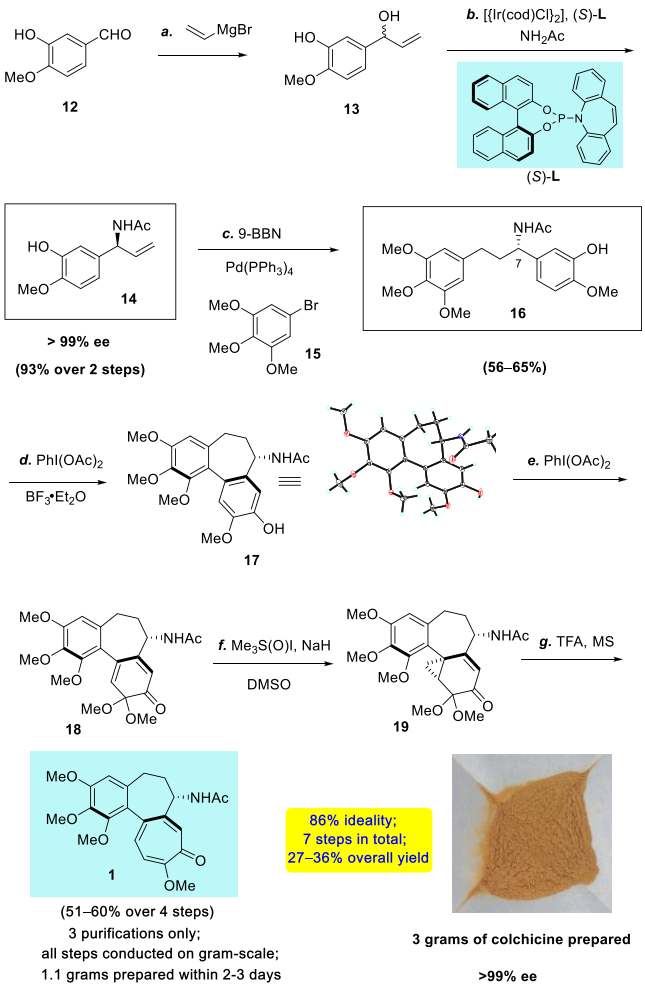
Scheme 1. Catalytic Asymmetric, Gram-Scale Synthesis of (−)-Colchicine[a]



[a]Reagents and conditions: (a) C_2H_3MgBr (4.0 equiv), THF, 0 °C; (b) $[\{Ir(cod)Cl\}_2]$ (3 mol %), (*S*)-**L** (12 mol %), NH_2Ac (2.0 equiv), $BF_3{\cdot}Et_2O$ (20 mol %), 1,4-dioxane, rt (93%, 2 steps, >99% ee); (c) 9-BBN (3.0 equiv), THF, 0 °C to rt; then H_2O (15.0 equiv), **15** (3.0 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (3.0 equiv), DMF, reflux (56–65%); (d) $PhI(OAc)_2$ (1.0 equiv), MeOH, rt; then $BF_3{\cdot}Et_2O$ (3.0 equiv), DCM, rt; (e) $PhI(OAc)_2$ (1.0 equiv), $NaHCO_3$ (2.0 equiv), MeOH, rt; (f) $Me_3S(O)I$ (1.0 equiv), NaH (1.1 equiv), DMSO, rt; (g) TFA (10.0 equiv), 4-Å molecular sieves, DCM, rt (51–60%, 4 steps).

found that the very pure crude product **13** of the first step could be subjected to Ir-catalyzed allylic amidation, also yielding allylic acetamide **14**.

After producing multigram quantities of **14**, we began the crucial Suzuki coupling.[11] Allylic acetamide **14** was converted to alkyl borane with 9-BBN in 4 h, which was coupled with commercially available 3,4,5-trimethoxylphenyl bromide (**15**) using the catalyst $Pd(PPh_3)_4$ to give a 56–65% yield of biphenyl compound **16** in 2 h. The fluctuation of the yield depended on the reaction scale. In addition, we believe that the yield could still be improved. Intramolecular oxidative coupling of **16** turned out to be a workable process after optimization of the conditions (see the SI). Treatment of **16** with PIDA and $BF_3{\cdot}Et_2O$ at room temperature for 35 min resulted in an 80% yield of allocolchicinoid **17**. **17** was a crystalline compound whose absolute configuration was confirmed by means of X-ray crystallographic analysis (CCDC 1981454) and was in agreement with the expected Ir-catalyzed selectivity. It is noteworthy that the foregoing steps are all construction reactions. To our knowledge, in contrast with the previous syntheses that required 10–20 steps,[3] this 4-step process stands for the most efficient means for allocolchicinoid preparation to date.

Treatment of allocolchicinoid **17** with PIDA in methanol at room temperature provided the expected cyclohexadienone **18** with an 84% yield in 5 min. Because this step was a strategic redox reaction, it also contributed to the synthetic ideality, as did other construction reaction steps.[7] Additionally, the adoption of environmentally friendly reagent PIDA rather than highly toxic $Pb(OAc)_4$ and $Tl(NO_3)_3$ used stoichiometrically in Banwell's route merits attention. Nucleophilic cyclopropanation of compound **18** with dimethylsulfoxonium methylide[12] proceeded both regio- and stereoselectively to rapidly result in an 82% yield of a single tetracyclic product **19** within 10 min. The resulting cyclopropane's configuration was tentatively assigned because it could not be established unequivocally with NMR techniques, and a single crystal of compound **19** could not be acquired. Regardless, this was inconsequential because the axial chirality of **1** was thermodynamically controlled by the configuration of the C-7 acetamido group,[5k] which had been confirmed using X-ray crystallographic analysis. Further treatment of tetracycle **19** with TFA in DCM produced colchicine (**1**) along with an unrearranged product caused by the simple hydrolysis of acetal, which was efficiently inhibited using a 4-Å molecular sieve (see the SI). Eventually, an 85% yield of colchicine (**1**) was obtained after heating at 40 °C for 2 h. The latter process could be carried out without intermediate purification, yielding 51–60% of colchicine (**1**) over four steps. Our synthetic colchicine (**1**) was identical in all respects to a natural sample.[13] In this laboratory, 3 g of colchicine samples can be synthesized in a short time.

In summary, a concise, catalytic asymmetric, and bioinspired total synthesis of (−)-colchicine was achieved. Salient features of the synthesis included the following: (1) efficiently addressing two key problems simultaneously for the first time using a highly efficient Ir-catalyzed amidation to install the C-7 acetamido group in a single operation with a high-yielding, bioinspired transformation to colchicine in the final step; (2) super ideality compared to previous syntheses, with the natural product being obtained in 7 steps/reactions, with 27–36% overall yield and 86% ideality, and all reactions were conducted on the gram-scale with only 3 steps requiring purification; (3) time economy—over 1 g of colchicine was prepared from 1.5 g of isovanillin by a single chemist in a single batch within 2–3 days. Such is the efficacy of this route that it could compete with the biosynthetic pathway which contains more than 20 transformations from amino acids. We do not think this work would be the end point of the total synthesis of colchicine. Other issues such as lowering the effective iridium catalyst loading and looking for a higher-yielding method of constructing biphenyl **16** are well worth considering if large-scale production is executed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00638.

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Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1981454 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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[§]X.L. and L.L. contributed equally.

Notes

The authors declare no competing financial interest.

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(13) To exclude partial racemization at the benzylic C7 acetamido group, we determined the ee value of our synthesized sample and found it remains unchanged (>99%).

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