## EDGE ARTICLE

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# Enantioselective total syntheses of six natural and two proposed meroterpenoids from *Psoralea corylifolia*†

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The first enantioselective total syntheses of six natural and two proposed meroterpenoids isolated from *Psoralea corylifolia* have been achieved in 7–9 steps from 2-methylcyclohexanone. The current synthetic approaches feature a high level of synthetic flexibility, stereodivergent fashion and short synthetic route, thereby providing a potential platform for the preparation of numerous this-type meroterpenoids and their *pseudo*-natural products.

Synthetic strategies play a central role in the total syntheses of natural products; therefore, numerous synthetic strategies have been developed, such as diversity-oriented synthesis, function-oriented synthesis, two-phase synthesis, convergent synthesis, modular synthesis, C–H bond functionalization, and so on.[1] Although considerable advances in these regards have been made, the pursuit of "ideal synthesis"[2] has been attracting attention from synthetic chemists to continually explore new synthetic strategies, including the innovative applications of existing synthetic methodologies.

The carbonyl group is one of the most fundamental functionalities in organic chemistry,[3] either as a crucial scaffold in countless organic molecules or as a universal and valuable reactive linchpin in synthetic chemistries. Due to its polarized C=O bond and the resultant acidic proton at the α-position of the carbonyl and/or the activation of the β-position through the formation of enolization-related reactive species, carbonyl-based chemical conversions have been an essential topic in organic synthesis, spawning numerous venerable organic reactions, particularly at the *ipso*-, α-, and β-positions of the carbonyl group.[4] These excellent achievements of carbonyl conversions serve as a great reservoir for designing and developing novel transformations in the total syntheses of natural products.[5] To add "a drop water" in "the ocean" of carbonyl-based conversion synthetic strategies, in the current work we

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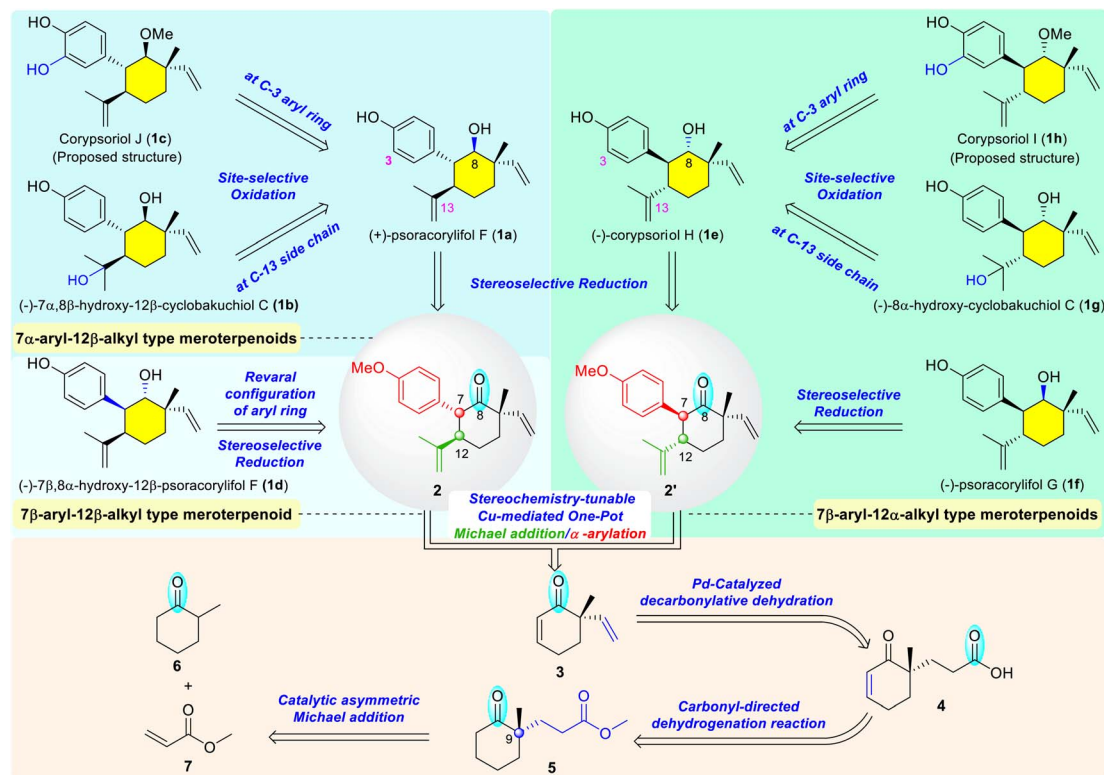
pursued the collective total syntheses of natural meroterpenes using such a strategy.

Meroterpenoids of the monoterpene phenol family were isolated from *Psoralea corylifolia*, a well-known medicinal plant that has been widely used for the treatment of various diseases in China, India, and other countries.[6] Some representative natural meroterpenes are shown in Scheme 1, including (+)-psoracorylifol F (**1a**),[7a] (−)-7α,8β-hydroxy-12β-cyclobakuchiol C (**1b**),[7c] corypsoriol J (**1c**),[7b] (−)-7β,8α-hydroxy-12β-psoracorylifol F (**1d**),[7c] (−)-corypsoriol H (**1e**),[7b] (−)-psoracorylifol G (**1f**),[7f] (−)-8α-hydroxy-cyclobakuchiol C (**1g**),[7c] corypsoriol I (**1h**),[7b] and other analogues.[7] Structurally, these meroterpenes possess a densely functionalized cyclohexane containing four contiguous chiral centers, with one of which being all-carbon stereocenter. Besides the distinct stereochemistry of the substituents at C-7, C-8, and C-12 positions, they also feature a diversity of oxidation states for the sidechain at C-12 position as well as the aryl ring at C-7 position. Therefore, they may serve as an ideal arsenal to interpret the magic of the stereodivergent synthesis.[1n] To the best of our knowledge, the total syntheses of these meroterpenes bearing four contiguous stereogenic centers have not been achieved to date.[8] Inspired by the unique structural features of the abovementioned meroterpenes and our research interest in carbonyl-related synthetic chemistry,[9] we designed a carbonyl-based conversion synthetic strategy and anticipated that these target molecules could be collectively synthesized through sequential transformations directed by the carbonyl group of synthetic intermediates in each crucial step (Scheme 1). Guided by this strategy, we speculated that the structural simplification of all target meroterpenes **1a–1h** to the key common intermediate **2** or its diastereomer **2′** would be feasible. For the 7α-aryl-12β-alkyl series, the hydroxy group at the C-13 position of 7α,8β-hydroxy-12β-cyclobakuchiol C (**1b**) or the C-3 position of corypsoriol J (**1c**) would be introduced *via*
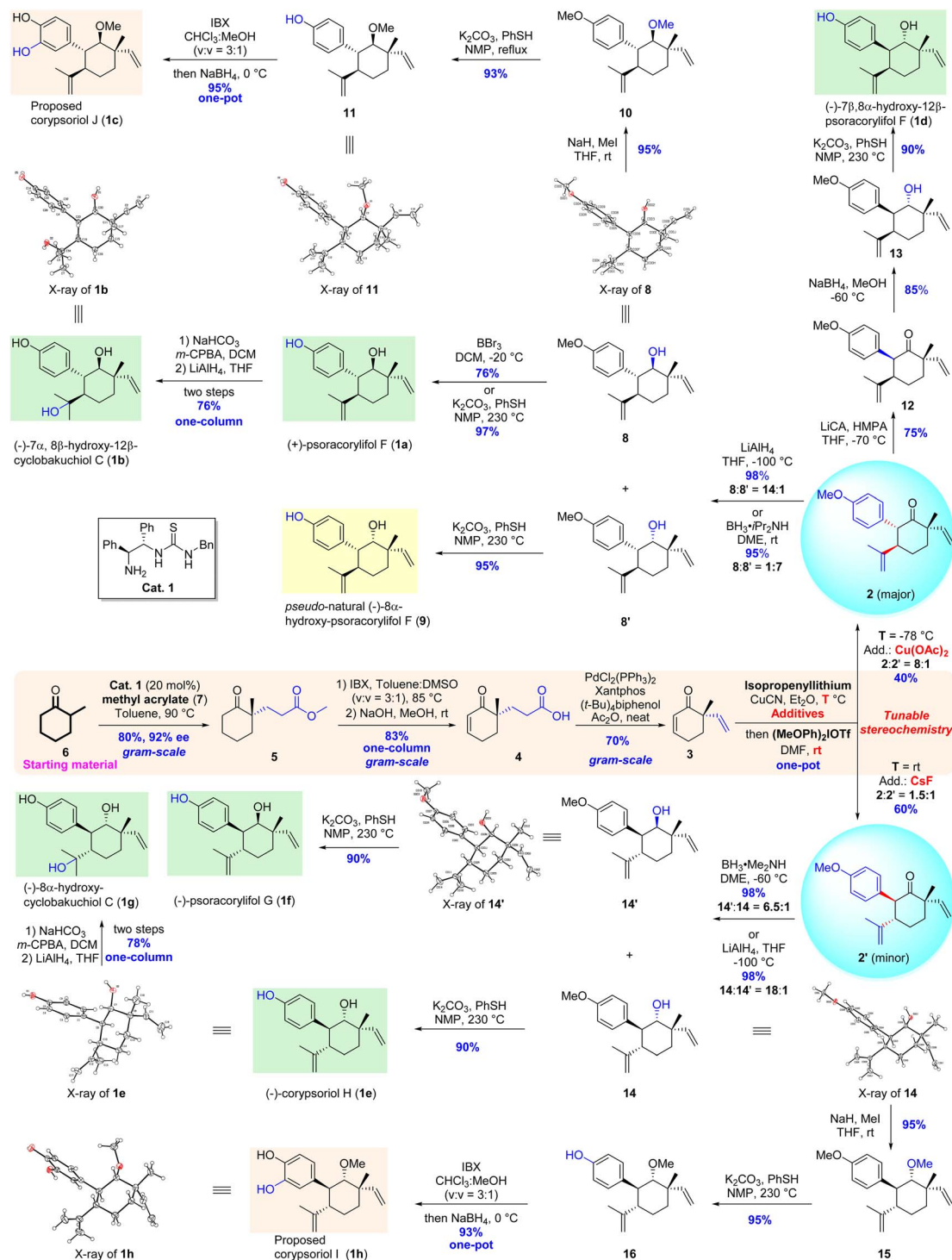
Scheme 1 The retrosynthetic analysis of meroterpenes using carbonyl-based conversions.

site-selective oxidation from psoracorylifol F (**1a**) or its C-8 methylether (not shown), respectively. Psoracorylifol F (**1a**), in turn, might be obtained *via* stereoselective reduction from the intermediate **2**. For 7β-aryl-12β-alkyl meroterpenes, such as 7β,8α-hydroxy-12β-psoracorylifol F (**1d**), the stereochemistry of the aryl ring could be reversed through an *in situ* carbonyl-mediated enolization/protonation process from the intermediate **2**; the β-hydroxyl group at the C-8 position would be acquired by the subsequent stereoselective reduction of the carbonyl group. Comparably, the 7β-aryl-12α-alkyl series, such as corypsoriol H (**1e**), psoracorylifol G (**1f**), 8α-hydroxy-cyclobakuchiol C (**1g**), and corypsoriol I (**1h**), could be achieved as well *via* similar transformations employing compound **2′**, a diastereomer of intermediate **2**, as the key precursor. The aryl ring at the C-7 position and transformable isopropenyl substituent at the C-12 position of the desired intermediates **2** and **2′** would be simultaneously assembled, in a stereochemistry-tunable fashion, using our developed Cu-mediated one-pot Michael addition/α-arylation reaction from enone **3**.[9a] Inspired by the excellent work of Stoltz,[10] the vinyl group of enone **3** would be generated through the Pd-catalyzed decarbonylative dehydration of acid **4**. The conjugated double bond in the acid **4** would be introduced by the carbonyl-based regioselective dehydrogenation of the δ-keto ester **5**. The all-carbon quaternary center at the C-9 position of δ-keto ester **5** would be constructed by the catalytic asymmetric Michael addition of the enolate of 2-methylcyclohexanone **6** to methyl acrylate **7**.

Following our retrosynthetic considerations, we commenced our total synthesis with the installation of the quaternary stereogenic centers of the target molecules. Using a modification of the method described by Cheong and Carter,[11] an intermolecular Michael addition between commercially available 2-methylcyclohexanone (**6**) and methyl acrylate (**7**) catalyzed by a chiral thiourea catalyst (Cat. **1**) afforded the expected adduct **5** with excellent enantiomeric excess (92% ee) and yield (80%) (Scheme 2). The conjugated double bond was introduced *via* carbonyl-directed dehydrogenation.[12] Although the classical enolization and subsequent oxidation developed by Saegusa[13] led to the desired desaturated enone **5′** (not shown, 65% yield),[14] 1.0 equivalent amount of Pd(OAc)$_2$ was necessary to achieve the complete conversion of the starting material **5**. Hence, a one-step approach using a stoichiometric amount of 2-iodoxybenzoic acid (IBX) as an oxidant[15] was examined. To our delight, δ-keto ester **5** was smoothly converted to the corresponding conjugated enone **5′** (86% yield), which was then hydrolyzed to release the acid **4** in 97% yield.[14] To further improve the synthetic efficiency, a two-step/one-column protocol was applied, affording the acid **4** in 83% yield. Subsequently, the Pd-catalyzed decarbonylative dehydration conditions developed by Stoltz[10] were employed to introduce a vinyl group at the C-9 position, and the expected enone **3** was smoothly obtained in 70% yield. After the introduction of a vinyl group at the quaternary carbon center on the cyclohexenone skeleton, we turned our attention to the assembly of vicinal difunctionalities of the precursors **2** and **2′** from enone **3**. Our

**Scheme 2** Collective total syntheses of meroterpenes from *Psoralea corylifolia*.

developed Cu-mediated one-pot Michael addition/α-arylation sequence was extensively investigated by varying the reaction temperature, the amount of the diaryliodonium salt, copper salts, additives, and reaction solvent.[14] Under the optimal reaction conditions, the expected product **2** along with its isomer **2′** was isolated in good stereoselectivity (8 : 1 dr) with moderate yield (40%, two-steps in one-pot). At this stage, the expected functionalities, including three chiral centers and one

transformable carbonyl group, were efficiently assembled in the cyclohexane skeleton through five-step asymmetric transformations from two chemical feedstocks. With the key intermediate **2** in hand, we continued our efforts to achieve the collective total syntheses of representative target meroterpenes.

The oxidation state at the C-8 position of precursor **2** was adjusted by reduction with LiAlH$_4$ in tetrahydrofuran (THF) at −100 °C to produce the major 8β-OH alcohol **8** and its minor

isomer **8′** with excellent levels of selectivity (14 : 1 dr) and yield (98%), while the selectivity was reversed (1 : 7 dr with 95% yield) using $BH_3 \cdot iPr_2NH$ as a reductant in 1,2-dimethoxyethane (DME) at room temperature. The structure of alcohol **8** was further confirmed by X-ray crystallographic analysis, in which the absolute configurations of the four stereogenic centers were unambiguously verified. Subsequently, the treatment of alcohol **8** with $BBr_3$ in $CH_2Cl_2$ removed the methyl ether at the aryl ring to afford (+)-psoracorylifol F (**1a**) in 76% yield, and an improved yield (97%) was observed when a combination of PhSH and $K_2CO_3$ in $N$-methylpyrrolidone (NMP) at 230 °C was applied.[16] Pleasingly, the spectral data of **1a** were consistent with the reported literature.[7a] Hence, the first total synthesis of (+)-psoracorylifols F was achieved in just 7 steps (Scheme 2). A similar deprotection of the methylether of the product **8′** yielded *pseudo*-natural (−)-8α-hydroxy-psoracorylifol F (**9**).

The site-selective epoxidation of the disubstituted double bond of (+)-psoracorylifol F with $m$-chloroperoxybenzoic acid ($m$-CPBA) and the subsequent reduction of the resulting epoxide with $LiAlH_4$ produced natural (−)-7α,8β-hydroxy-12β-cyclobakuchiol C (**1b**) in 76% yield (two steps), and its structure was also confirmed by X-ray crystallographic analysis (Scheme 2).

To achieve the total synthesis of corypsoriol J (**1c**), alcohol **8** was treated with MeI to produce methylether **10** in 95% yield. The selective removal of methyl phenol ether was then examined, and the expected phenol **11** was obtained in excellent yield (93%) using the PhSH/$K_2CO_3$/NMP reaction system.[16] To install an OH group at the C-3 position of the aryl ring, a two-step one-pot transformation[17] involving IBX-mediated oxidation and subsequent reduction of the resultant *ortho* diketone with $NaBH_4$ yielded the proposed corypsoriol J (**1c**) (95% yield) (Scheme 2). Unfortunately, the spectral data of synthetic corypsoriol J were not consistent with the reported ones of the natural product.[7b] Efforts to obtain the X-ray crystallographic structures of the synthetic corypsoriol J and its three derivatives were not successful.[14] However, subsequent synthetic endeavors further confirmed that the structure of the proposed corypsoriol J needs to be revised.

Due to 7β,8α-hydroxy-12β-psoracorylifol F (**1d**) featuring a *cis*-configuration of the aryl ring at the C-7 position and an alkyl substituent at the C-12 position, a one-pot protocol involving the enolization/protonation of the key precursor **2** was carried out to reverse the configuration of the aryl ring. The desired product **12** was obtained in 75% yield using lithium isopropylcyclohexylamide (LiCA) as a base in THF at −70 °C, along with a recovery of the precursor **2** (10% yield). The subsequent stereoselective reduction of the carbonyl group of compound **12** generated alcohol **13** as a single isomer (85% yield), without the isolation of another diastereoisomer. The demethylation of **13** completed the total synthesis of (−)-7β,8α-hydroxy-12β-psoracorylifol F (**1d**) in 90% yield, and its spectral data were consistent with those of the corresponding natural product[7c] (Scheme 2).

Having accomplished the total syntheses of two natural 7α-aryl-12β-alkyl meroterpenoids, a proposed one, a *pseudo*-natural product, along with a 7β-aryl-12β-alkyl meroterpenoid, we focused on a third set of meroterpenoids, namely, 7β-aryl-12α-

alkyl substituted natural products **1e–1h** (Scheme 2), whose C-7 and C-12 stereocenters are reversal compared with the synthetic compounds **1a–1c**. Fortunately, these natural meroterpenoids possess the same configuration of the minor product **2′** obtained from the previous key one-pot Michael addition/α-arylation reaction. Therefore, the tuning of the selectivity of the one-pot reaction is important. Various reaction conditions were again investigated to optimize the selectivity; the best results were obtained with an acceptable amount of product **2′** and its isomer **2** (ratio = 1 : 1.5, 60% combined yield for two steps).[14] With the desired precursor **2′** in hand, chemical transformations similar to those for the syntheses of target molecules **1a–1c** were performed to complete the total syntheses of four 7β-aryl-12α-alkyl substituted meroterpenoids. The stereoselective reduction of the carbonyl group at the C-8 position with $LiAlH_4$ in THF at −100 °C provided two isomers **14** and **14′** with an excellent level (18 : 1 dr); in contrast, the treatment of **2′** with $BH_3 \cdot Me_2NH$ in DME at −60 °C resulted in reverse selectivity, affording isomers **14′** and **14** (6.5 : 1 dr). The demethylation of compounds **14** and **14′** yielded (−)-corypsoriol H (**1e**) and (−)-psoracorylifol G (**1f**), respectively. The site-selective epoxidation of (−)-corypsoriol H and subsequent reductive ring-opening of the resultant epoxide completed the total synthesis of (−)-8α-hydroxy-cyclobakuchiol C (**1g**) in 78% yield (two steps). The spectroscopic data of these three synthesized natural products were fully consistent with those reported in the literature, respectively.[7b,c,f] Finally, using an approach similar to that for the proposed corypsoriol J, corypsoriol I (**1h**) was also synthesized in 4 steps with 66% overall yield from the precursor **2′**. Its chemical structure was unambiguously confirmed by X-ray crystallographic analysis. Unfortunately, the spectral data of synthetic corypsoriol I were also not consistent with the reported literature[7b] (Scheme 2). Therefore, the chemical structures of natural corypsoriols I and J need to be reassigned.

In summary, the first enantioselective total syntheses of six meroterpenoids, *i.e.* (+)-psoracorylifol F, (−)-7α, 8β-hydroxy-12β-cyclobakuchiol C, (−)-7β, 8α-hydroxy-12β-psoracorylifol F, (−)-corypsoriol H, (−)-psoracorylifol G, and (−)-8α-hydroxy-cyclobakuchiol C, and two proposed corypsoriols I and J, along with *pseudo*-natural (−)-8α-hydroxyl-psoracorylifol F, have been accomplished using a carbonyl-based conversion synthetic strategy to install all stereogenic centers and the corresponding functionalities. The key transformations include organocatalytic Michael addition to construct a quaternary carbon center, Nicolaou oxidation to yield an enone, Pd-catalyzed decarbonylative dehydration to introduce a vinyl group, one-pot Michael addition/α-arylation to assemble two vicinal stereocenters, epimerization to reverse the configuration of the aryl group, and stereoselective reduction of ketone to acquire hydroxyl groups with different C-8 configurations. We envision that our stereodivergent synthetic route for the meroterpenoids reported here will facilitate further investigation of the biological activities of natural products, *pseudo*-natural ones, and their non-natural analogues. Further extension of this carbonyl-based conversion synthetic strategy for the total

synthesis of natural products is being carried out in our laboratory.

## Data availability

The datasets and spectra supporting this article have been uploaded as part of the ESI material.† Crystallographic data for compounds **1b**, **1e**, **1h**, **8**, **11**, **14** and **14′** have been deposited in the Cambridge Crystallographic Data Center under accession numbers CCDC 2226760 (**1b**), CCDC 2226749 (**1e**), CCDC 2226751 (**1h**), CCDC 2226753 (**8**), CCDC 2226754 (**11**), CCDC 2226756 (**14**), and CCDC 2226759 (**14′**).†

## Author contributions

F.-M. Z. designed the project and wrote the manuscript. X.-W. C., Z.-C. H., C. C., and L.-H. Z. performed all the experiments. X.-W. C. prepared the ESI.† L.-H. Z. and M.-E. C. prepared some starting material and part of the ESI.† All of the authors discussed the results.

## Conflicts of interest

There are no conflicts to declare.

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