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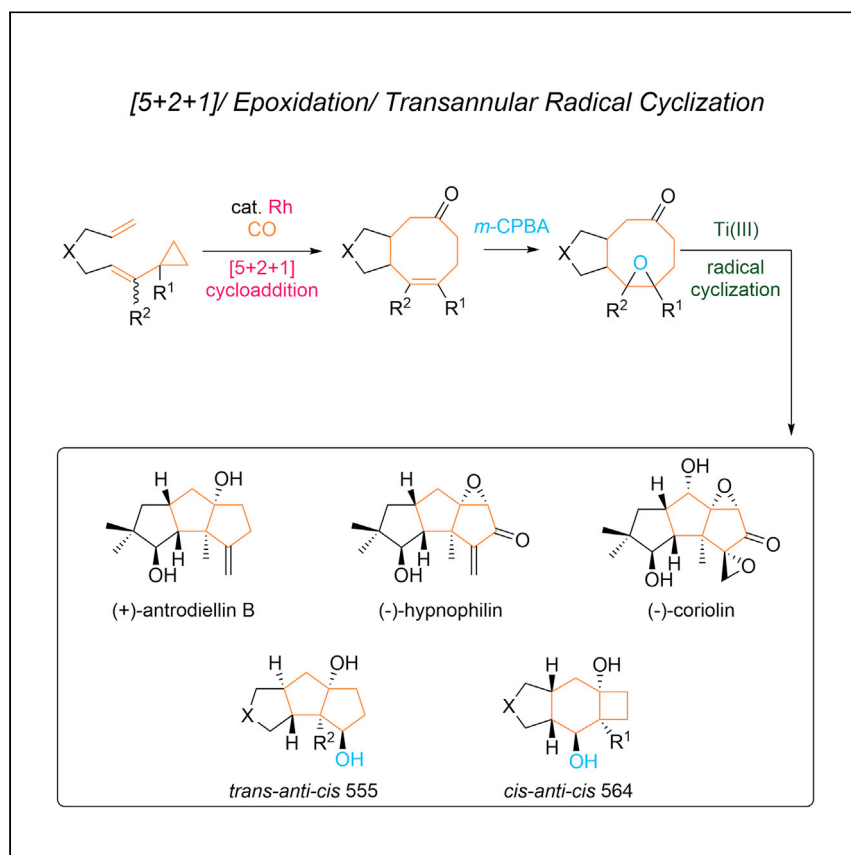
Antrodiellin B/hypnophilin/coriolin and strained 5/5/5 and 5/6/4 skeletons via [5+2+1]/epoxidation/transannular radical cyclization

[5+2+1]/ Epoxidation/ Transannular Radical Cyclization

(+)-antrodiellin B

(−)-hypnophilin

(−)-coriolin

trans-anti-cis 555

cis-anti-cis 564

Yu et al. develop a [5+2+1] cycloaddition/epoxidation/transannular radical cyclization strategy to achieve asymmetric synthesis of (+)-antrodiellin B, (−)-hypnophilin, and (−)-coriolin, all of which have a *cis-anti-cis*-configured 5/5/5 tricyclic skeleton. This strategy is also applied to access challenging *trans-anti-cis*-configured 5/5/5 and *cis-anti-cis*-configured 5/6/4 tricyclic skeletons.

Lu-Ning Wang, Zhiqiang Huang, Zhi-Xiang Yu

yuzx@pku.edu.cn

Highlights

Develop a strategy based on [5+2+1] reaction to access 5/5/5 and 5/6/4 skeletons

Realize asymmetric synthesis of antrodiellin B, hypnophilin, and coriolin

Article

Antrodiellin B/hypnophilin/coriolin and strained 5/5/5 and 5/6/4 skeletons via [5+2+1]/epoxidation/transannular radical cyclization

Lu-Ning Wang,[1] Zhiqiang Huang,[1] and Zhi-Xiang Yu[1,2,*]

SUMMARY

Many natural products contain compact *cis*-anti-*cis*-configurated 5/5/5 and 5/6/4 tricycles, and efficient access to these molecules is posing many hurdles to the synthetic community. Accessing molecules with more strained *trans*-anti-*cis*-configurated 5/5/5 tricycles (which are rarely found in nature) was envisioned to be more challenging, and no solution to this has been reported. We describe here a [5+2+1]/epoxidation/transannular radical cyclization strategy to solve the above-mentioned challenges, as demonstrated by the first total synthesis of (+)-antrodiellin B, the asymmetric total synthesis of (−)-hypnophilin, and the formal synthesis of (−)-coriolin, all of which contain a *cis*-anti-*cis*-configurated 5/5/5 skeleton, together with the synthesis of compounds with 5/6/4 and *trans*-anti-*cis*-configurated 5/5/5 tricycles. The present strategy is helpful for obtaining these and other molecules and their analogs for future downstream studies dependent on synthetic molecules with unusual scaffolds.

INTRODUCTION

Molecules containing linear 5/5/5[1,2] (called triquinanes) and 5/6/4[3–10] tricyclic structures are widely found in nature. Figure 1 gives several representative molecules in these families. Among them, (+)-antrodiellin B (**1**) was just recently isolated from wild fungus *Antrodiella albocinnamomea* last year.[2] Syntheses of these molecules have been receiving intensive interest from synthetic chemists.[11–16] One reason for this is that many of these natural products have attractive bioactivities and have the potential to become lead compounds for drug discovery. For example, (−)-hypnophilin (**2**), isolated from *Pleurotellus hypnophilus*,[17,18] shows 100% inhibition of trypanothione reductase (TR) at 4 μM and good anti-bacterial properties.[19] (−)-Coriolin (**3**), isolated from *Coriolus consors*,[20,21] has anti-bacterial properties and anti-tumor activities.[22] Another reason is that the challenging 5/5/5 tricyclic skeletons and the complex stereochemistry, substitutions, and oxidation states require chemists to design new reactions and strategies to conquer them. In the past decades, many elegant methods and strategies for constructing linear 5/5/5 structures have been developed. The strategies for these syntheses can be divided into three catagories (using syntheses of hypnophilin and coriolin as examples): (1) synthesizing three five-membered rings in proper sequences,[23–32] (2) synthesizing two or three five-membered rings by a cascade cyclization process in one step,[33–37] and (3) skeleton rearrangement.[38–46] Only a few of these reported strategies used transannular reactions (such as ene and aldol reactions) converting 5/8 bicycles, as precursors, to 5/5/5 ring systems (see examples from Pattenden, Wender, and List in Scheme 1).[47–52] This can be understood because preparation of eight-membered carbocycles was usually more challenging than direct synthesis of five-membered
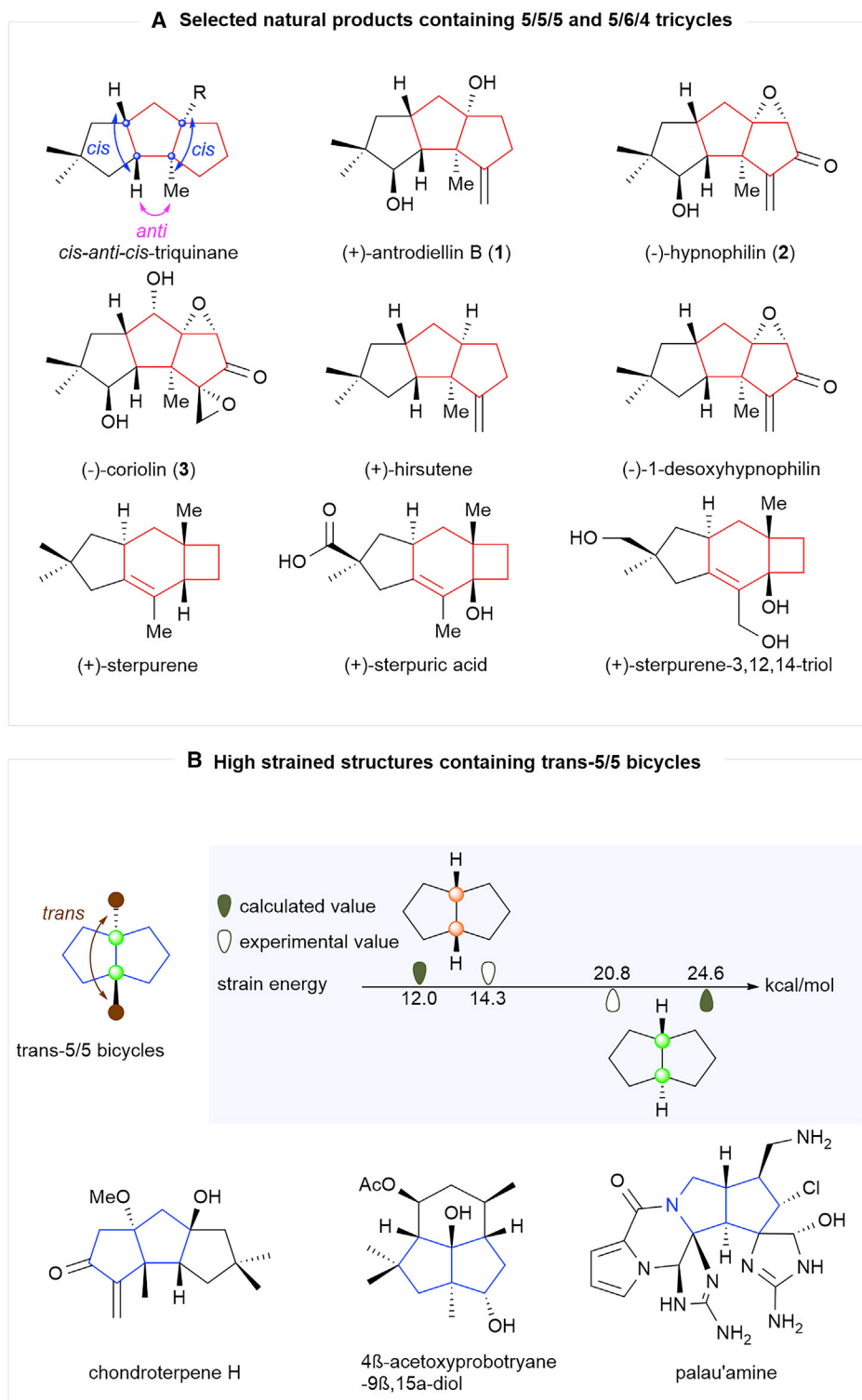
Figure 1. Selected natural products and high-strained *trans*-5/5 bicycles

(A) Some selected typical natural products containing *cis*-anti-*cis*-configurated 5/5/5 and 5/6/4 tricycles: triquinane-type sesquiterpenes and sterpurane-type sesquiterpenes.

(B) High-strained *trans*-5/5 bicycles and their comparison with *cis*-5/5 bicycles. Selected triquinane and other natural products contain difficultly prepared *trans*-5/5 bicycles.

rings.[53,54] But today, more methods and strategies of accessing eight-membered carbocycles have been discovered and developed,[55–57] implying that more transannular strategies now and in the future to reach 5/5/5 or other multicycles by using easily accessed 5/8 precursors would become viable. Actually, we previously developed three transannular strategies, all of which used 5/8 precursors synthesized by the Rh-catalyzed [5+2+1] reaction,[58,59] followed by either an aldol reaction[49] or an ene reaction,[51,52] to access 5/5/5 tricyclic skeletons (Scheme 1).

It is interesting to find that nature has also generated many strained molecules with bent arene, anti-Bredt double bond, and *trans*-configured 5/5 bicycles.[60] Among them, natural products with *trans*-configured 5/5 bicycles are found, and some of them have shown significant bioactivities. Three examples in this family are given in Figure 1B.[61–64] With the previous successes in building 5/5/5 tricycles, we challenged ourselves to design new transannular reactions to reach not only the common 5/5/5 rings but also other strained rings such as *trans*-anti-*cis*-configured 5/5/5 and 5/6/4 tricycles. With this in mind, we then decided to use Ti(III)-mediated radical cyclization to test our ideas, considering that this Ti(III)-mediated cyclization can build strained structures, as demonstrated by many leading synthetic chemists in their pursuits of the syntheses of natural products.[65–75]

Our design is outlined in Scheme 2A. First, a rhodium-catalyzed [5+2+1] cycloaddition was used to form *cis*- or *trans*-5/8 bicycles. In this reaction, linear substrate ene-vinylcyclopropanes (ene-VCPs) (**4**) reacted with CO to generate the desired compounds (**5**) with a cyclooctenone moiety in good yields. If the R^2 group was not an H atom, both the *cis*- or *trans*-5/8 bicycles (***cis*-5** and ***trans*-5**) can be obtained by the [5+2+1] cycloaddition, depending on the configuration of the C–C double bond in the VCP moiety of substrates **4**. Usually, the *Z*-configured ene-VCPs gave the *cis*-5/8 bicycles, while *E*-configured ene-VCPs gave the *trans*-5/8 bicycles. If the R^2 group was an H, both the *E*-and *Z*-configured ene-VCP substrates **4** gave the *cis*-5/8 bicyclic products.

Then, cycloadducts **5** were subjected to an epoxidation reaction, followed by a trivalent-titanium-mediated transannular reaction to deliver tricyclic diols **7** or **8**. The reaction mechanism for this is given in Scheme 2B. Epoxides **6** could react with Ti(III) reagent to form a carbon radical and an alkoxyl Ti(IV) species (**I** or **II**). Then, the cyclization products, tricyclic diols (**7** or **8**), can be obtained from an intramolecular radical cyclization reaction via the newly generated carbon radicals attacking the carbonyl group in the eight-membered ring. We hypothesized that the selectivity of the newly generated carbon radical can be adjusted by the substituent R^1 and R^2 on the substrates: 5/5/5 tricyclic diols **7** would be obtained when R^1 = H, and R^2 is a substituent, while 5/6/4 tricyclic diols **8** could be accessed when R^1 is a substituent, but R^2 = H. Here, we report the results of synthesizing these strained molecules by using the [5+2+1]/epoxidation/transannular radical cyclization sequence. The power of this strategy was further demonstrated in the target-oriented syntheses of three 5/5/5 natural products of (+)-antrodiellin B, (−)-hypnophilin, and (−)-coriolin, which is also described in this article.

RESULTS AND DISCUSSION

Syntheses of *cis*-anti-*cis*-configured 5/5/5 tricyclic diols

According to the design, we synthesized *cis*-5/8 bicycle **5a** with R_1 = Me (Figure 2). Then, epoxidation of **5a** with *m*-CPBA generated **6a** in 95% yield. After that, **6a** was treated with the trivalent titanium (prepared by 3 equiv Cp_2TiCl_2 and 6 equiv Zn
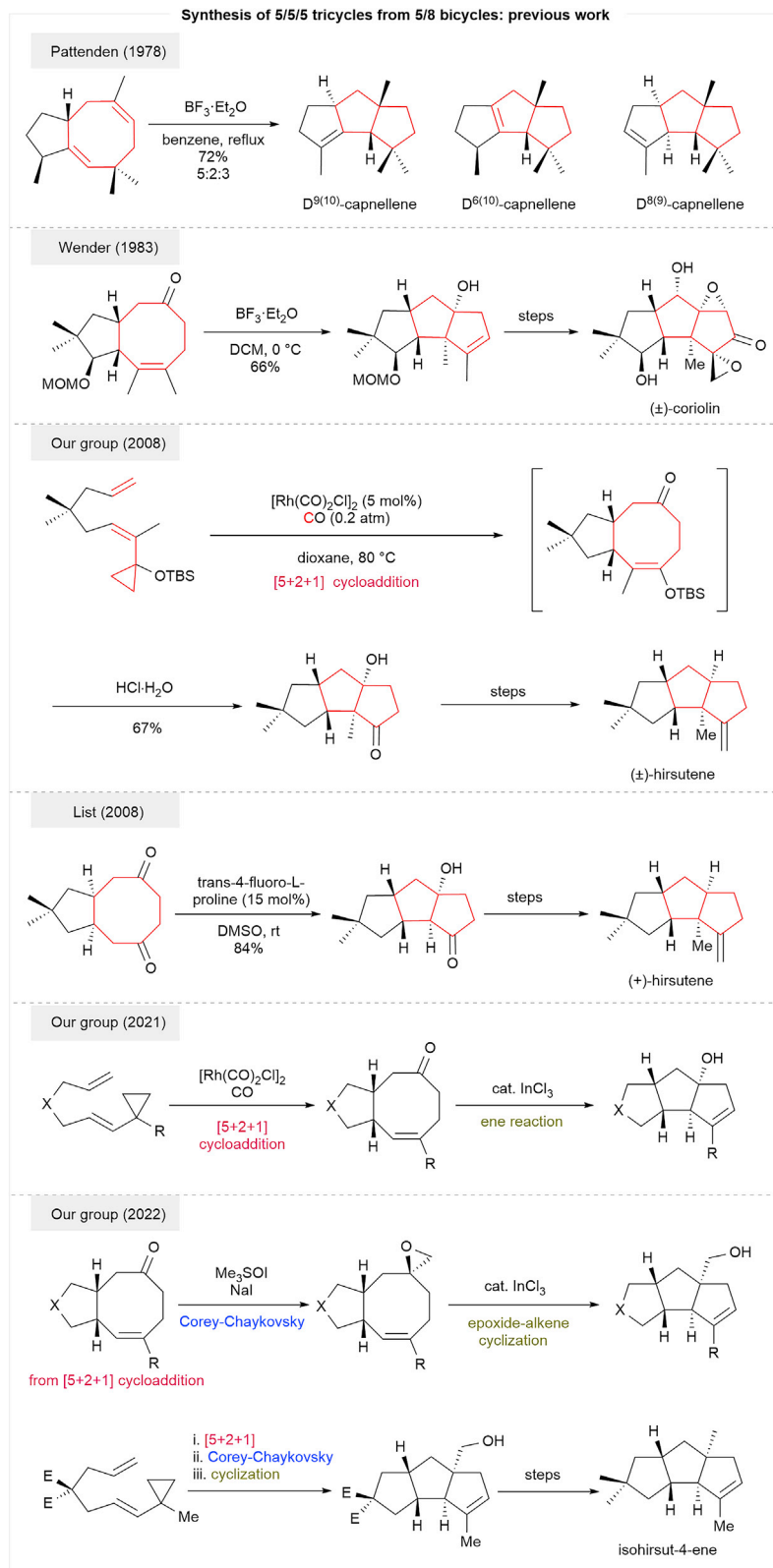
Scheme 1. Previous methods and strategies to construct 5/5/5 tricycles through transannular cyclizations of 5/8 bicycles
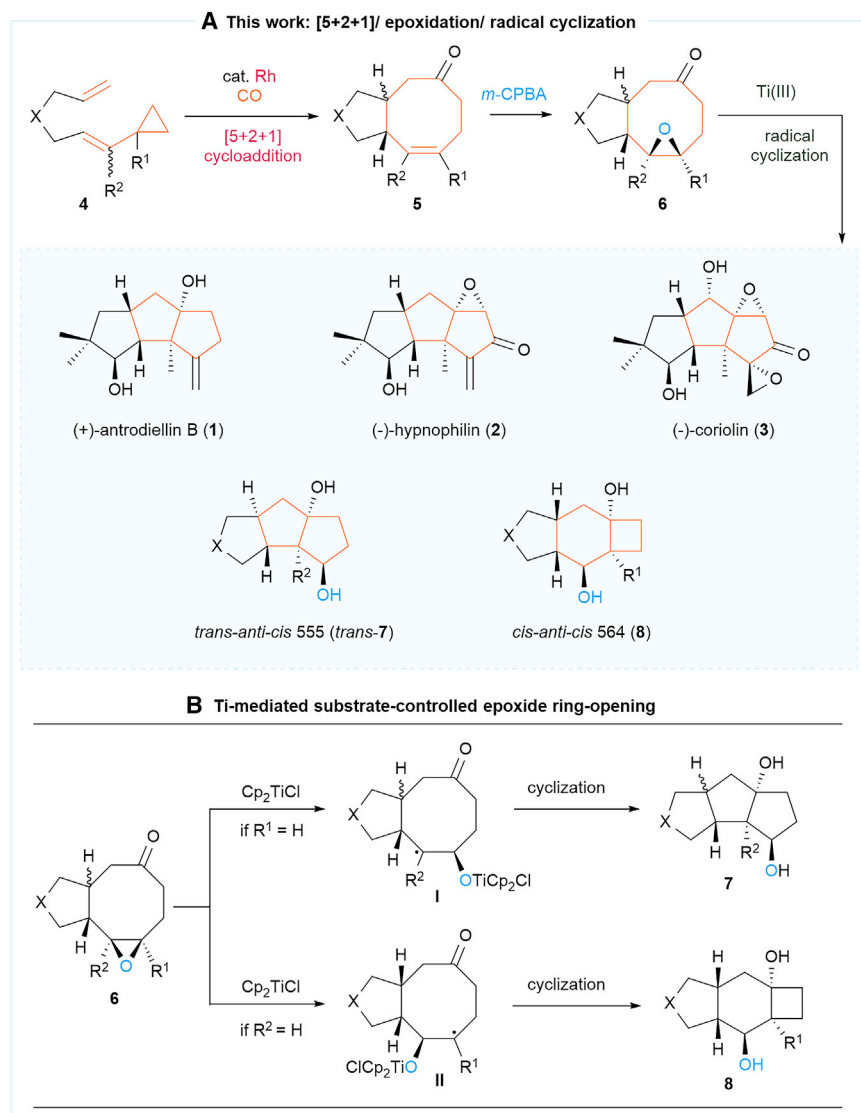
Scheme 2. Substrate-controlled epoxide ring opening and follow-up cyclization to two types of tricycles

(A) The [5+2+1]/ epoxidation/ transannular strategy.

(B) The Ti-mediated epoxide ring-opening.

powder *in situ*), and the desired tricyclic product **7a** was obtained smoothly at room temperature in 76% yield. The structure of **7a** with a *cis*-anti-*cis* 5/5/5 configuration (two substituent groups on the bridgehead positions of fused 5/5 bicycles were in *cis*-configuration, and two adjacent groups on bridgehead position of one fused bicycle with another one adopted anti-configuration) was confirmed by the X-ray diffraction analysis of its analog, compound **26**, which was obtained from another *cis*-5/8 bicycle **13** (see later discussion). This success prompted us to apply this strategy to the syntheses of natural products (+)-antrodiellin B, (−)-hypnophilin, and (−)-coriolin, which is presented in the final part of this paper.

Syntheses of *trans*-anti-*cis*-configurated 5/5/5 tricyclic diols

Since our [5+2+1] cycloaddition can also deliver *trans*-5/8 products when using substrates with *Z*-configurated VCP, we wondered whether the above transannular
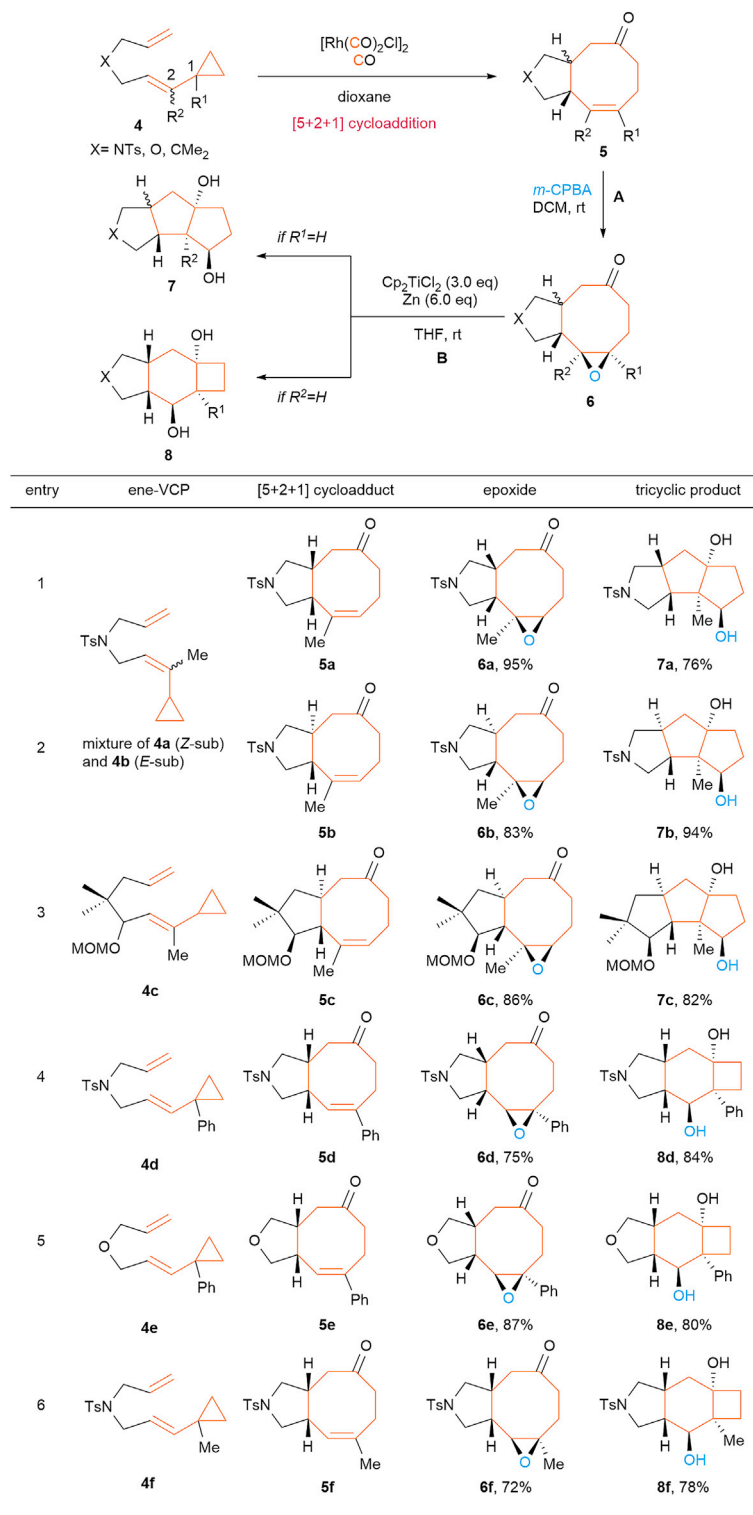
Figure 2. Scope of substrates to tricyclic products

(A) Reaction conditions: [5+2+1] cycloadduct (ca. 0.35 mmol, 1 equiv), *m*-CPBA (3 equiv), DCM (0.05 M), room temperature (RT).

(B) Reaction conditions: epoxide (0.1 mmol, 1 equiv), Cp₂TiCl₂ (3 equiv), Zn (6 equiv), THF (0.033 M), RT.

approach could be used to synthesize *trans-anti-cis* 5/5/5 tricycles. Therefore, we converted **4c** (dimethyl-tethered ene-*E*-VCP with a methoxymethoxyl [MOMO] group) to the *trans*-5/8 product **5c**, which was then converted to epoxide **6c** in 86% yield. To our delight, *trans*-5/8 epoxide **6c** can generate successfully the desired *trans-anti-cis* tricyclic diol **7c** under the same reaction conditions mentioned above (Figure 2). The structure of **7c** was confirmed by X-ray diffraction of its *p*-bromobenzoyl analog **9** (Scheme 3). Besides, N-tethered substrate **5b** can also give the desired *trans-anti-cis* 5/5/5 product **7b** as a single diastereomer by applying the same strategy.

Syntheses of *cis-anti-cis* 5/6/4 tricyclic diols

Now, we describe here how we built a 5/6/4 skeleton by the above transannular approach. We synthesized the *cis*-5/8 product **4d** by the [5+2+1] reaction, which was then converted to epoxide product **5d**. To our delight, a transannular radical reaction of **5d** treated with trivalent titanium can take place to give 5/6/4 compound **8d** (Figure 2). The *cis-anti-cis* configuration of **8d** was proposed by analogy to compound **10**, confirmed by X-ray analysis (Scheme 3). Besides, O-tethered substrate **4e** and methyl-substituted substrate **4f** can, respectively, be converted to 5/6/4 products **8e** and **8f**. Therefore, the present strategy is very effective in obtaining analogs of natural products with 5/6/4 skeletons for medicinal investigation. Usually, oxygen-centered radicals in four-membered rings prefer to undergo Grob fragmentation to form bigger rings,[76] but here, it is the opposite. We attributed this to the thermodynamic reason, proposing that once the oxygen radical is generated, it can be trapped by Ti(III) to form a strong O–Ti bond[66,72] (excess Ti(III) was used in the reaction). More examples for the synthesis of 5/6/4 and other strained molecules with appropriate substituents can be envisioned with the above proof of concept. With the above successes, we then focused on using this strategy to do total synthesis, which is presented below.

Syntheses of (+)-antrodiellin B, (−)-hypnophilin, and (−)-coriolin

Three natural products, (+)-antrodiellin B (**1**), (−)-hypnophilin (**2**), and (−)-coriolin (**3**), with tricyclic cores were the targets of total synthesis. The retrosynthetic analysis is shown in Scheme 4, where the key intermediate is tricyclic compound **11**, which was previously used by Paquette,[46] Curran,[37] and Weinges[77,78] in their syntheses of hypnophilin and coriolin. In our synthesis, intermediate **11** could be synthesized from tricyclic diol **12**, which can be accessed via the [5+2+1]/epoxidation/cyclization strategy. At the same time, antrodiellin B can be easily prepared via the intermediate **12**. The [5+2+1] cycloadduct **13** can be reached from substrate ene-VCP **14**, which must have a *Z*-configuration in order to have a *cis-anti-cis* configuration in product **13**. We planned to use a chiral substrate **14** for the synthesis so that we could achieve the synthesis of the target molecules in an asymmetric fashion.

Here, we detail our synthesis. The easily prepared *Z*-configurated cyclopropyl allyl alcohol **17** was oxidized by MnO_2 in DCM, delivering the *α,β*-unsaturated aldehyde **18**, with retention of the double-bond configuration in the product. Then, **18** reacted with (2-methylpent-4-en-2-yl)lithium **16** to produce racemic ene-VCP **rac-19** with the retention of the VCP configuration. Here, **16** was prepared by a decyano-lithiation reaction, which was developed by Overman and coworkers,[79] from 2,2-dimethylpent-4-ene-nitrile **15** using lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB)[80] through a reduction reaction. To get chiral substrate **19**, we oxidized the racemic **19** to its ketone, followed by CBS reduction using (*S*)-CBS. To our delight, chiral compound **19** was obtained in 81% yield and 97% *ee*. The hydroxyl group in **19** was protected by the methoxymethyl (MOM) group, and the resulting product **14** was then subjected to our traditional
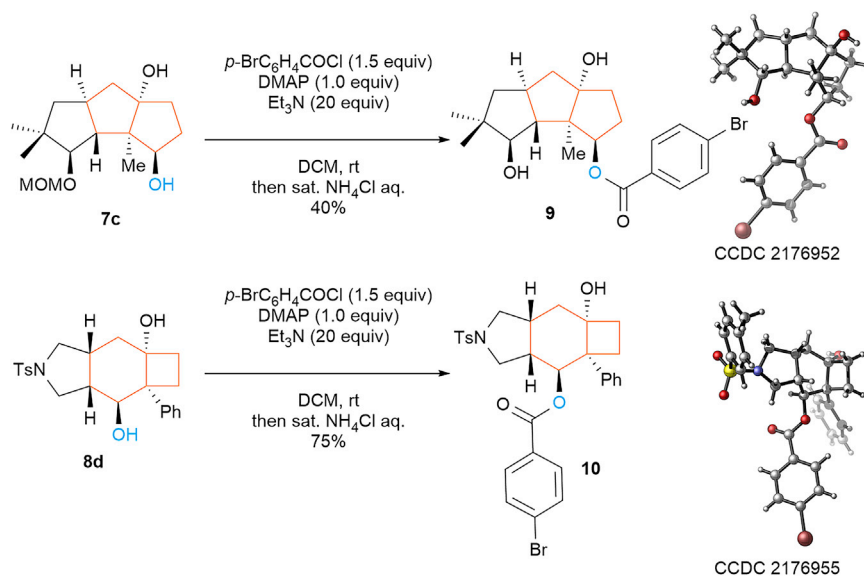
Scheme 3. X-ray structures of *trans*-anti-*cis*-configured 5/5/5 tricycle and *cis*-anti-*cis*-configured 5/6/4 tricycle

[5+2+1] reaction conditions. We were happy to observe that the target chiral 5/8 product **13** was obtained in 49% yield as a single diastereoisomer (Figure 3).

We then carried out the epoxidation/transannular radical cyclization strategy by using **13**. Epoxide **20** can be obtained in 87% yield from **13**. Then, **20** was added to the solution of Cp$_2$TiCl$_2$ and Zn powder in THF for the transannular radical reaction. To our delight, the reaction worked well and gave the desired 5/5/5 tricyclic diol **12** in 84% yield. The absolute configuration and the structure of this product were determined by X-ray diffraction of its *p*-bromobenzoyl analog **26** (Figure 3).

The followed tasks in the total synthesis include oxidation state adjustments and functional group transformations. Compound **12** could be oxidized by pyridinium dichromate (PDC) to compound **21**, which was then converted by Wittig olefination to compound **22**. Then, we planned that the total synthesis of (+)-antrodiellin B (**1**) could be completed via the deprotection of intermediate **22**.[81] Unfortunately, we obtained compound **23** instead of **1**, suggesting that a double-bond isomerization took place under acidic conditions. Due to this, we reversed the order of these two reactions by removing the MOM group firstly, generating intermediate **24**, followed by Wittig olefination to give (+)-antrodiellin B (**1**). The ^{1}H, ^{13}C nuclear magnetic resonance (NMR) and specific optical rotation of the synthesized product here matched perfectly with those of this natural product (Figure 3).

We then continued our journey to synthesize another two natural products from **22**. Allylic oxidation reaction of **22** by using SeO$_2$/t-BuOOH gave an alcohol, which was then oxidized by Dess-Martin periodinane (DMP) to deliver compound **25**. Under the acidic conditions, α,β-dehydration and deprotection of the MOM group were realized in one pot, giving rise to the desired advanced intermediate **11**. The ^{1}H, ^{13}C NMR spectra and specific optical rotation of this synthesized compound were identical to those reported in the literature. Intermediate **11** was then epoxidized to give (−)-hypnophilin in 29% yield using H$_2$O$_2$ (together with the recovered 63% starting material). The ^{1}H, ^{13}C NMR and specific optical rotation of the synthesized product
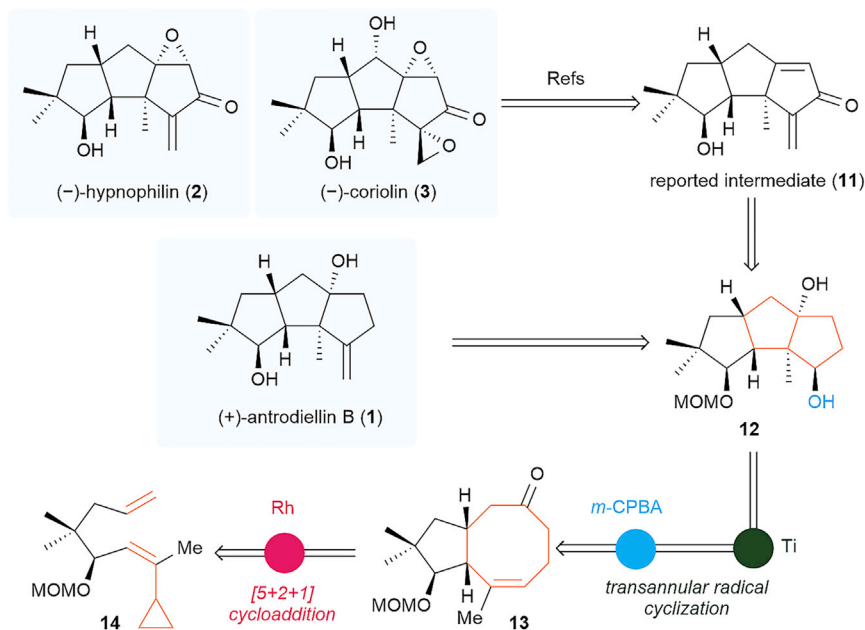
Scheme 4. Retrosynthetic analysis of (+)-antrodiellin B, (−)-hypnophilin, and (−)-coriolin based on [5+2+1]/epoxidation/radical cyclization strategy

here matched perfectly with those of this natural product. From intermediate **11**, (−)-coriolin could be synthesized by using an additional 4 steps reported by Paquette et al. With these, we accomplished the asymmetric total synthesis of (−)-hypnophilin (**2**) and the formal total synthesis of (−)-coriolin (**3**) (Figure 3).

In summary, we developed a [5+2+1] cycloaddition/epoxidation/transannular radical cyclization strategy to synthesize molecules with three kinds of tricyclic skeletons, including (1) a regular *cis*-anti-*cis*-configurated 5/5/5 tricyclic skeleton that exists widely in linear triquinane-type natural products or hetero-triquinane natural products; (2) a synthetically challenging *trans*-anti-*cis*-configurated 5/5/5 tricyclic skeleton containing a high-strained *trans*-fused bicyclo[3.3.0] octane structure; and (3) a *cis*-anti-*cis*-configurated 5/6/4 tricyclic skeleton. We also used this strategy to realize the asymmetric total synthesis of (+)-antrodiellin B and (−)-hypnophilin and the formal synthesis of (−)-coriolin in high efficiency. We believe such a transannular approach could be applied to other big ring compounds so that various compact and strained polycyclic molecules can be realized.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Zhi-Xiang Yu(yuzx@pku.edu.cn).

Materials availability

All data supporting this study are available in the supplemental information or are available upon request from the lead author.

Data and code availability

All the characterization data and experimental protocols are provided in this article and its supplemental information. See Figure S1 and Tables S1 and S2 for density
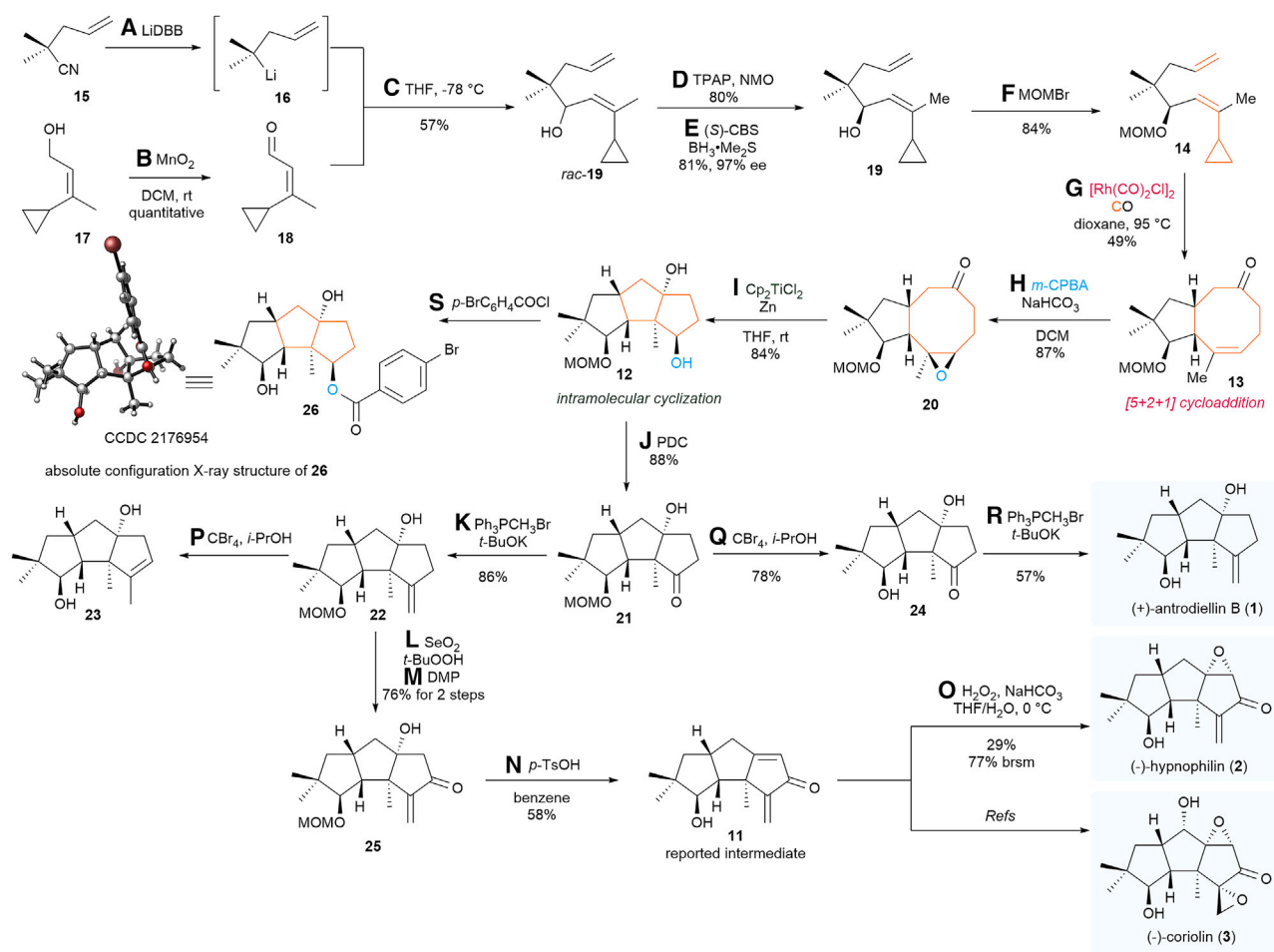
Figure 3. Asymmetric syntheses toward (+)-antrodiellin B, (−)-hypnophilin, and (−)-coriolin

Reagents and conditions: (A) LiDBB (0.4 M, 1.5 equiv), THF, 0°C; (B) active MnO$_2$ (10 equiv), DCM, RT; (C) aldehyde (1 equiv), tertiary lithium reagent (4 equiv), THF, −78°C; (D) TPAP (5 mol %), NMO (1.5 equiv), DCM, RT; (E) (S)-Me-CBS (1 M in toluene, 1 equiv), BH$_3$·Me$_2$S (5 equiv), toluene, −30°C; (F) MOMBr (4 equiv), DIPEA (20 equiv), DCM, 0°C; (G) [Rh(CO)$_2$Cl]$_2$ (10 mol %), CO (0.2 atm, CO:N$_2$ = 1/4 v/v), 1,4-dioxane, 95°C; (H) m-CPBA (75%, 1.5 equiv), NaHCO$_3$ (3 equiv), DCM, RT; (I) Cp$_2$TiCl$_2$ (3 equiv), Zn (6 equiv), THF, RT; (J) PDC (2 equiv), 4 Å MS, DCM, RT; (K) Ph$_3$PCH$_3$Br (5 equiv), t-BuOK (6 equiv), toluene/t-BuOH = 5/1, 100°C; (L) SeO$_2$ (0.7 equiv), t-BuOOH (3 equiv), DCM, RT; (M) DMP (1.5 equiv), NaHCO$_3$ (1.5 equiv), DCM, RT; (N) p-TsOH, benzene, 50°C; (O) H$_2$O$_2$, NaHCO$_3$, THF, H$_2$O, 0°C; (P) CBr$_4$ (0.49 equiv), i-PrOH, 80°C; (Q) CBr$_4$ (1.1 equiv), i-PrOH, 80°C; (R) Ph$_3$PCH$_3$Br (24 equiv), t-BuOK (24 equiv), THF, RT; (S) acid silica gel, then p-BrC$_6$H$_4$COCl (2 equiv), TEA, DCM, RT.

LiDBB, lithium 4,4′-di-tert-butylbiphenylide; TPAP, tetrapropyl-ammonium perruthenate; NMO, 4-methylmorpholine N-oxide; (S)-Me-CBS, (S)-2-Methyl-CBS-oxazaborolidine; DIPEA, N,N-diisopropylethylamine; m-CPBA, 3-chloroperbenzoic acid; Cp$_2$TiCl$_2$, titanocene dichloride; PDC, pyridinium dichromate; RT, room temperature.

functional theory (DFT) studies. Crystallographic data have been deposited at the Cambridge Crystallographic Data Center, under deposition numbers CCDC: 2176952 (compound **9**), 2176955 (compound **10**), and 2176954 (compound **26**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

General procedure for Ti-mediated cyclization of epoxide to tricycles

To a flask with Cp$_2$TiCl$_2$ (3.0 equiv) and Zn powder (6.0 equiv) was added THF (1.5 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature for 30 min to generate a dark green suspension. A solution of epoxide of [5+2+1] cycload-duct (1.0 mmol, 1.0 equiv) in THF (1.5 mL) was added and stirred for another 4 h at room temperature. Then, the reaction mixture was quenched with water and extracted with

Et$_2$O. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated by rotary evaporation. Purification of the crude product by flash column chromatography afforded cyclization tricyclic product.

Further details can be found in the supplemental experimental procedures.

AUTHOR CONTRIBUTIONS

Z.-X.Y. designed and supervised the project, L.-N.W. and Z.H. designed and carried out the chemical reactions and analyzed the data, and Z.-X.Y., L.-N.W., and Z.H. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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