Syntheses of (+)-Antrodiellin B, (−)-Hypnophilin and (−)-Coriolin and Strained 5/5/5 and 5/6/4 Skeletons via [5+2+1]/ Epoxidation/ Transannular Radical Cyclization

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ABSTRACT: Nature produces many molecules (so-called natural products) containing compact scaffolds such as *cis-anti-cis*-configurated 5/5/5 and 5/6/4 tricycles. But other molecules with more strained structures, such as *trans-anti-cis*-configurated 5/5/5 tricycles have been rarely found in nature. Accessing all these natural and non-natural molecules will strengthen the power of organic synthesis and benefit many fields such as medicinal chemistry, chemical biology that are heavily dependent on the available quantity of new/important molecules. Herein, we report a new strategy to synthesize molecules with *cis-anti-cis*-configurated 5/5/5 tricycles, 5/6/4 tricycles and *trans-anti-cis*-configurated 5/5/5 tricyclic skeletons by [5+2+1]/epoxidation/transannular radical cyclization strategy, where challenging cis and trans 5/8 bicycles with both ene and carbonyl functional groups were accessed by Rh-catalyzed [5+2+1] reaction of ene-vinylcyclopropanes and carbon monoxide, followed by epoxidation of the double bond in the 5/8 bicycles, and Ti(III) mediated epoxide/carbonyl cyclization to build target skeletons. This strategy was further applied to the first total synthesis of (+)-antrodiellin B, the asymmetric total synthesis of (−)-hypnophilin and formal synthesis of (−)-coriolin with *cis-anti-cis* configurated 5/5/5 skeleton (both hypnophilin and coriolin are highly oxidized and have significant biological activities).

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* in this year.[11] Syntheses of these molecules have been receiving intensive interests from synthetic chemists.[12-17] One reason for this is that many of these natural products have attractive bioactivities and have potential to become lead compounds for drug discovery. For example, (−)-hypnophilin (**2**), isolated from *Pleurotellus hypnophilus*,[18-19] shows 100% inhibition of trypanothione reductase (TR) at 4 μM and good anti-bacterial properties.[20] (−)-coriolin (**3**), isolated from *Coriolus consors*,[21-22] has anti-bacterial properties and antitumor activities.[23] 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 devided into three catalogs (using syntheses of hypnophilin and coriolin as examples): (1) Synthesizing three five-membered rings in proper sequences,[24-33] (2) synthesizing two or three five-membered rings by a cascade cyclization process in one step,[34-38]and (3) skeleton rearrangement.[39-47] 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 Fig. 2).[48-53] This can be understood because preparation of eight-membered carbocycles was usually more challenging than direct synthesis of five-membered rings.[54-55] But today, more methods and strategies

of accessing eight-membered carbocycles have been discovered and developed,[56-58] 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 Rh-catalyzed [5+2+1] reaction,[59-60] followed by either an aldol reaction[50] or an ene reaction,[52-53] to access 5/5/5 tricyclic skeletons (Fig. 2).

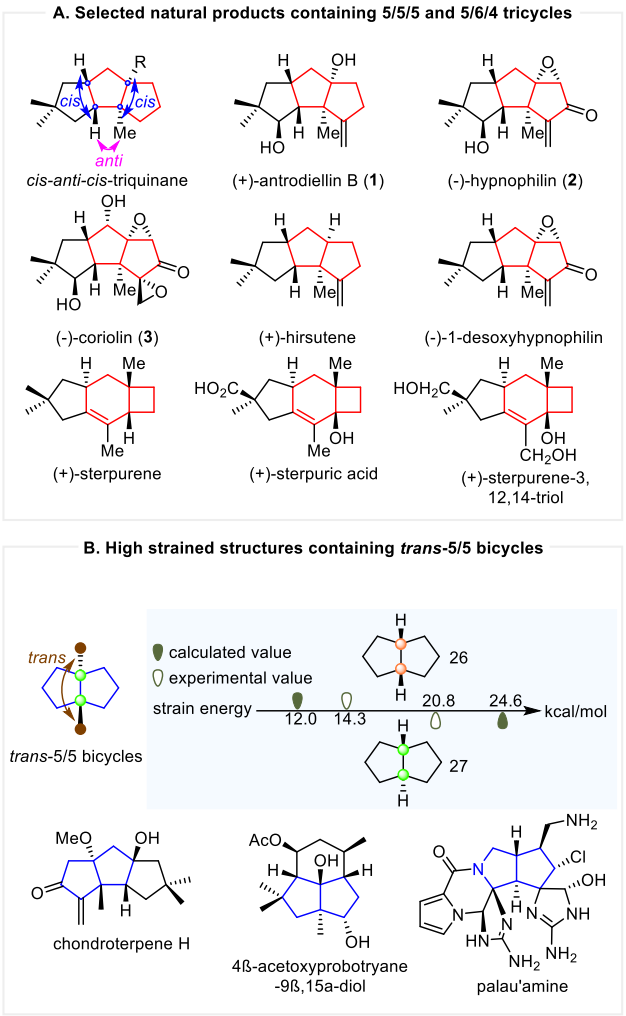


Fig. 1. | A. Some selected typical natural products containing *cis-anti-cis*-configurated 5/5/5 and 5/6/4 tricycles: triquinane-type sesquiterpenes and sterpurane-type sesquiterpenes. **B**. High strained *trans*-5/5 bicycles and their comparison to *cis*-5/5 bicycles. Selected triquinane and other natural products contain difficultly prepared *trans*-5/5 bicycles.

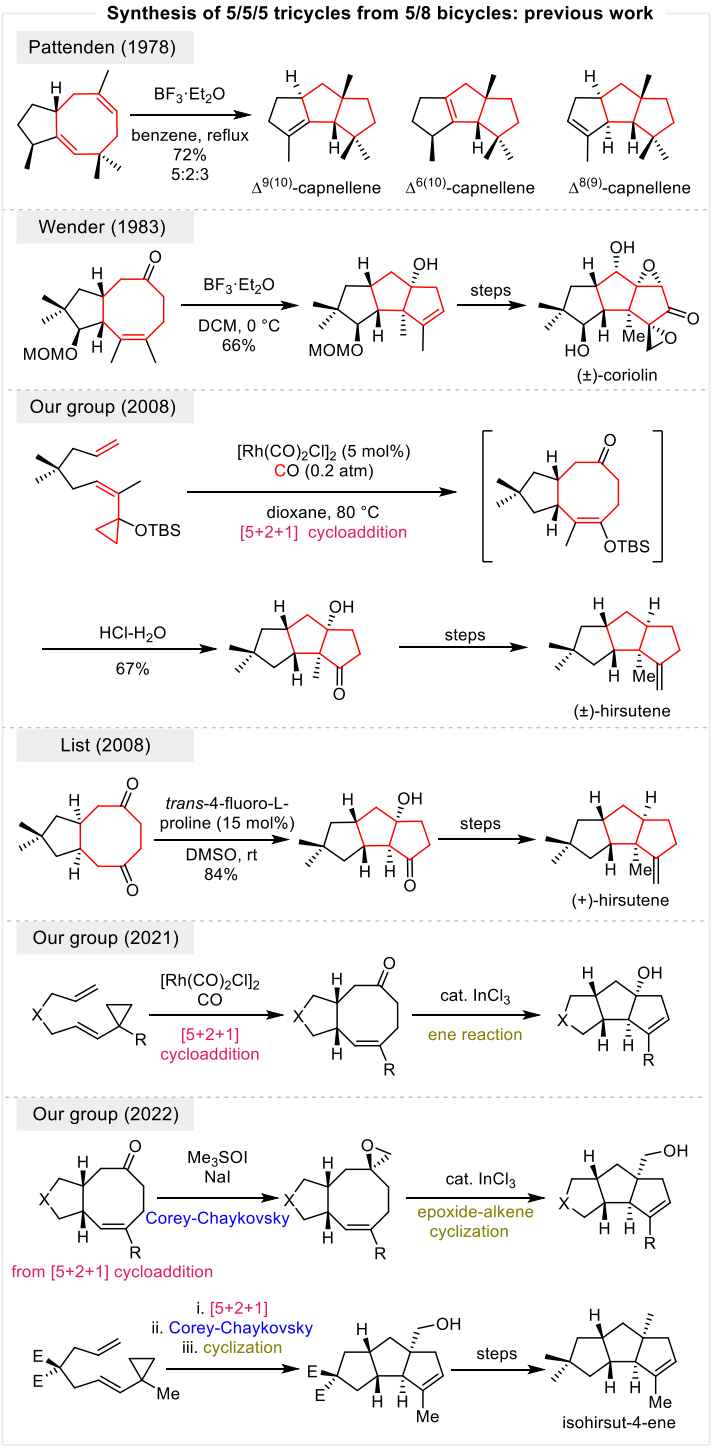


Fig. 2 | Previous methods and strategies to construct 5/5/5 tricycles through transannular cyclizations of 5/8 bicycles.

It is interesting to find that nature has also generated many strained molecules with bent arene, *anti*-Bredt double bond and *trans*-configurated 5/5 bicycles.[61] Among them, natural products with *trans*-configurated 5/5 bicycles are found and some of them have shown significant bioactivities. Three examples in this family are given in Figure 1B.[62-65] 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*-configurated 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.[66-76]

Our design was outlined in Fig. 3 A. 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 R^2 group was not 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 C−C double bond in the VCP moiety of substrates **4**. Usually, the *Z*-configurated ene−VCPs gave the *cis*-5/8 bicycles, while *E*-configurated ene−VCPs gave the *trans*-5/8 bicycles. If R^2 group was H, both the *E*- and *Z*-configurated ene−VCP substrate **3** gave the *cis*-5/8 bicyclic products.

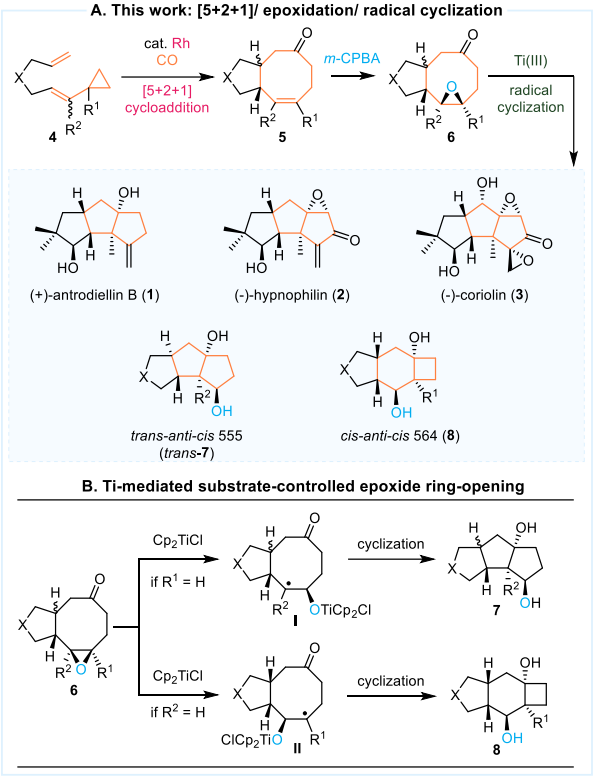


Fig. 3 | Substrate-controlled epoxide ring-opening and follow-up cyclization to two types of tricycles.

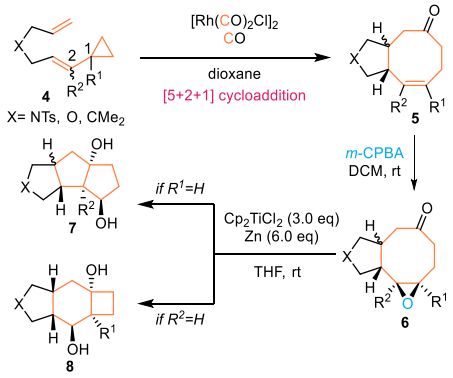
Then cycloadducts **5** were subjected to epoxidation reaction, followed by a trivalent-titanium mediated transannular reaction to deliver tricyclic diols **7** or **8**. The reaction mechanism for this is given in Fig. 3 B. Epoxides **6** could react with Ti(III) reagent to form a carbon radical and 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 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 paper.

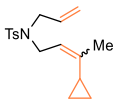
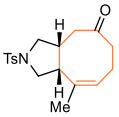
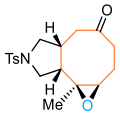
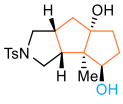
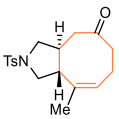
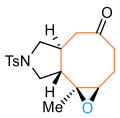
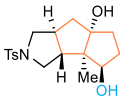
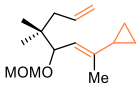
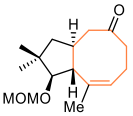
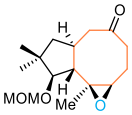
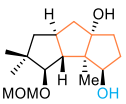
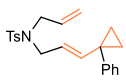
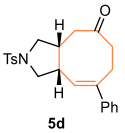
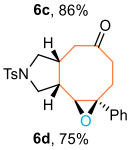
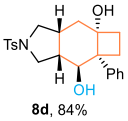
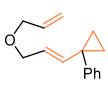
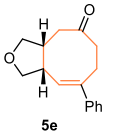
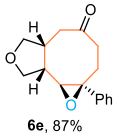
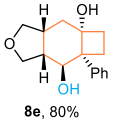
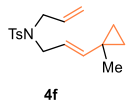
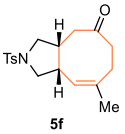
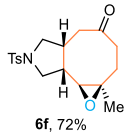
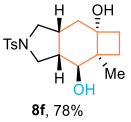
Results and Discussion

Syntheses of *Cis-anti-cis*-configurated 5/5/5 Tricyclic Diols. According to the design, we synthesized *cis*-5/8

bicycle **5a** with R_1=Me. Then epoxidation of **5a** with *m*-CPBA generated **6a** in 95% yield. After that, **6a** was treated with the trivalent titanium (prepared by 3 equivalents of Cp_2TiCl_2 and 6 equivalents of Zn 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.

Table 1. Scope of substrates to tricyclic products.



entry	ene-VCP	[5+2+1] cycloadduct	epoxide	tricyclic product
1		 **5a**	 **6a**, 95%	 **7a**, 76%
2	mixture of **4a** (*Z*-sub) and **4b** (*E*-sub)	 **5b**	 **6b**, 83%	 **7b**, 94%
3	 **4c**	 **5c**	 **6c**, 86%	 **7c**, 82%
4	 **4d**	 **5d**	 **6d**, 75%	 **8d**, 84%
5	 **4e**	 **5e**	 **6e**, 87%	 **8e**, 80%
6	 **4f**	 **5f**	 **6f**, 72%	 **8f**, 78%

[a] Reaction conditions: [5+2+1] cycloadduct (ca.0.35 mmol, 1.0 equiv), *m*-CPBA (3.0 equiv), DCM (0.05 M), rt. [b] Reaction conditions: epoxide (0.1 mmol, 1.0 equiv), Cp_2TiCl_2 (3.0 equiv), Zn (6.0 equiv), THF (0.033 M), rt. rt = room temperature.

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 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. Structure of **7c** was confirmed by X-ray diffraction of its *p*-bromobenzoyl analog **9**. 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.

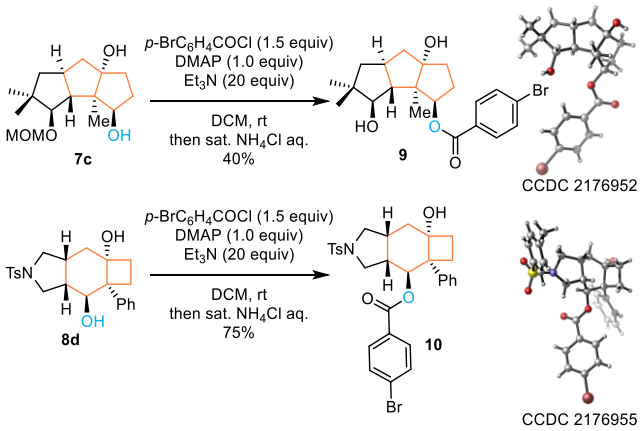


Fig. 4 | X-ray Structures of *trans-anti-cis*-configurated 5/5/5 tricycle and *cis-anti-cis*-configurated 5/6/4 tricycle

Syntheses of *Cis-anti-cis* 5/6/4 Tricyclic Diols. Now we describe here how we built 5/6/4 skeleton by the above transannular approach. We synthesized *cis*-5/8 product **4d** by the [5+2+1] reaction, which was then converted to epoxide product **5d**. To our delight, transannular radical reaction of **5d** treated with trivalent titanium can take place to give 5/6/4 compound **8d**. The *cis-anti-cis*-configuration of **8d** was proposed by analogy to compound **10**, confirmed by X-ray analysis (Fig. 4). 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,[77] but here 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 strong O−Ti bond[67,78] (excess Ti(III) was used in the reaction).

Syntheses of (+)-antrodiellin B, (−)-hypnophilin and (−)-coriolin. Having achieved three different kinds of tricyclic cores using the designed strategy, we further applied this method to the syntheses of three natural products, (+)-antrodiellin B (**1**), (−)-hypnophilin (**2**) and (−)-coriolin (**3**). The retrosynthetic analysis was shown in Fig. 5, where our key intermediate is tricyclic compound **11**, which was previously used by Paquette,[47] Curran[38] and Weinges[79,80] in their syntheses of hypnophilin and coriolin. In our synthesis, intermediate **11** could be synthesized from tricyclic diol **12**, which can be accessed via [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 can achieve the synthesis of the target molecules in an asymmetric fashion.

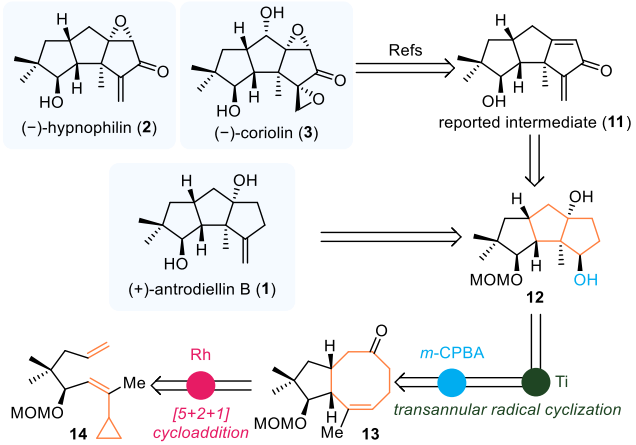


Fig. 5 | Retrosynthetic analysis of (+)-antrodiellin B, (−)-hypnophilin and (−)-coriolin based on [5+2+1]/ epoxidation/ radical cyclization strategy.

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,[81] from 2,2-dimethylpent-4-enenitrile **15** using lithium 4,4'-di-tert-butylbiphenylide (LiDBB)[82] through a reduction reaction. To get chiral substrate **19**, we oxided 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 MOM (methoxymethyl) group, and the resulting product **14** was then subjected to our traditional [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.

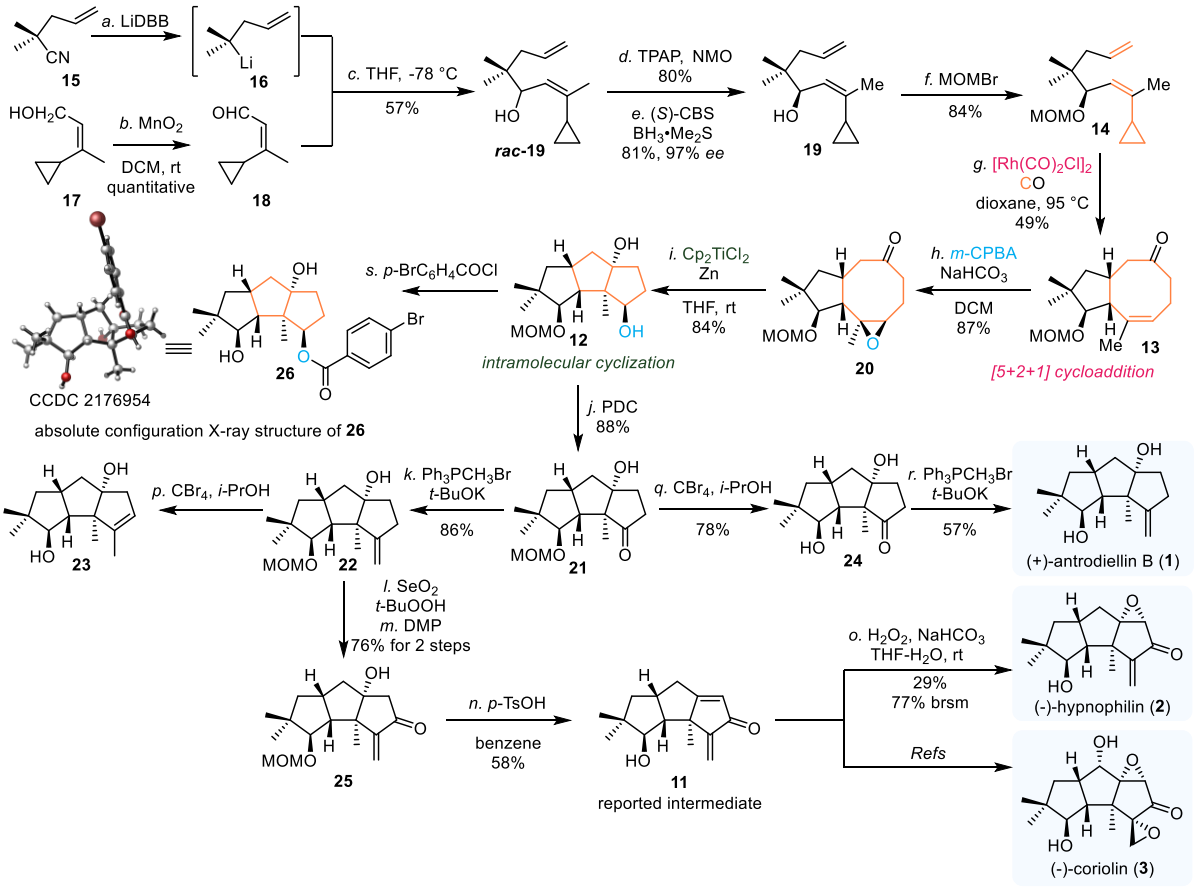


Fig. 6 | Asymmetric syntheses towards (+)-antrodiellin B, (−)-hypnophilin and (−)-coriolin. Reagents and conditions: [a] LiDBB (0.4 M, 1.5 equiv), THF, 0°C. [b] active MnO_2 (10 equiv), DCM, rt. [c] aldehyde (1.0 equiv), tertiary lithium reagent (4.0 equiv), THF, -78°C. [d] TPAP (5 mol%), NMO (1.5 equiv), DCM, rt. [e] (*S*)-Me-CBS (1.0 M in toluene, 1.0 equiv), $BH_3 \cdot Me_2S$ (5 equiv), toluene, -30°C. [f] MOMBr (4 equiv), DIPEA (20 equiv), DCM, 0°C. [g] $[Rh(CO)_2Cl]_2$ (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), $NaHCO_3$ (3.0 equiv), DCM, rt. [i] Cp_2TiCl_2 (3 equiv), Zn (6 equiv), THF, rt. [j] PDC (2.0 equiv), 4Å MS, DCM, rt. [k] Ph_3PCH_3Br (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_2O_2, $NaHCO_3$, THF, H_2O, 0 °C. [p] CBr_4 (0.49 equiv), *i*-PrOH, 80°C. [q] CBr_4 (1.1 equiv), *i*-PrOH, 80°C. [r] Ph_3PCH_3Br (24 equiv), *t*-BuOK (24 equiv), THF, rt. [s] acid silica gel, then *p*-BrC6H4COCl (2.0 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_2TiCl_2=titanocene dichloride, PDC=pyridinium dichromate. rt=room temperature

We then carried out 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_2TiCl_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 6).

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**.[83] 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 NMR and specific optical rotation of the synthesized product here matched perfectly with those of this natural product.

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 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 with those reported in literature. Intermediate **11** was then epoxidized to give (−)-hypnophilin in 29% yield using H_2O_2 (together with the recovered 63% starting material). The ^{1}H, ^{13}C NMR and specific optical rotation of the synthesized product here matched perfectly with those of this natural product. From intermediate **11**, (−)-coriolin could be synthesized by using additional 4 steps reported by Paquette et al. With these, we accomplished the asymmetric total synthesis of (−)-hypnophilin (**2**) and formal total synthesis of (−)-coriolin (**3**).

Conclusion

In summary, we developed a [5+2+1] cycloaddition/ epoxidation/ transannular radical cyclization strategy to synthesize molecules with three kinds of tricyclic skeletons, including (i) regular *cis-anti-cis*-configurated 5/5/5 tricyclic skeleton which exists widely in linear triquinane-type natural products or hetero-triquinane natural products; (ii) synthetically challenging *trans-anti-cis*-configurated 5/5/5 tricyclic skeleton containing a high-strained *trans*-fused bicyclo[3.3.0] octane structure; (iii) *cis-anti-cis*-configurated 5/6/4 tricyclic skeleton. We also used this strategy to realize the asymmetric total synthesis of (+)-antrodiellin B, (−)-hypnophilin and 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 multicyclic molecules can be realized.

Data availability

All the characterization data and experimental protocols are provided in this article and its Supplementary Information. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, under deposition number CCDC 2176952 (compound **9**), CCDC 2176955 (compound **10**) and CCDC 2176954 (compound **26**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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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, Z.-X.Y., L.-N.W. and Z.H. wrote the manuscript.

Additional information

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