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New facile enantio- and diastereo-selective syntheses of (–)-triptonide and (–)-triptolide†

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Hongrui Zhang,[a] Haifeng Li,[a] Jijun Xue,[a] Rui Chen,[a] Ying Li,*[a] Yu Tang*[a] and Chunxin Li[b]

A novel formal asymmetric synthesis of (–)-triptonide and (–)-triptolide, featuring a new alternative access to their known key intermediate 4, has been achieved through two synthetic routes in 9 steps with 13.6% total yield and 10 steps with 18.5% overall yield, respectively. This synthesis is scalable and hence has high potential for application to further synthetic elaboration and biologic investigation on such natural products.

Synthetic chemists have been focusing on the development of efficient and elegant chemical processes for the rapid synthesis of highly functionalized, structurally diverse, and architecturally complex bioactive compounds from simple starting materials.[1] So applying facile transformations in total synthesis to get elegant schemes becomes the main strategy. (–)-Triptolide (**1**),[3] (–)-triptonide (**2**), and (+)-triptophenolide (**3**)[2] are interesting diterpenoid epoxides found in the Thunder God Vine, *Tripterygium wilfordii*, and their highly-functionalized *trans*-fused-tetracyclic skeleton with multiple chiral centers represents a challenging aspect of the total synthesis. Biologically, such molecules have interestingly shown extraordinary activities against pancreatic cancer cells. Additionally, the triptolide also showed *in vitro* and *in vivo* activity in mouse models of polycystic kidney disease, which is a cystic genetic disorder of kidneys and can damage the liver, pancreas and, in rare cases, the heart and the brain, and so it is one of the most common life-threatening genetic diseases affecting an estimated 12.5 million people worldwide.[4] Furthermore, some compounds derived from triptolides have shown remarkable activities and great potential; for example, 5-hydroxytriptolide, a derivative of triptolide (**1**), has been used in clinical trials.[5]

The important biological properties[6–8] and interesting structures of these compounds from the Thunder God Vine have made them attractive as synthetic[9–11] and medicinal targets.[7] Many studies have been devoted to these syntheses. G. A. Berchtold[9] and E. E. van Tamelen[10] have reported the racemic synthesis of the triptolide. Yang[11a–e] and Li[11f] reported the enantioselective syntheses of triptonide and triptolide. Some synthetic efforts[12] have also been made to access the analogues. However, it is still a great challenge for chemists to efficiently and elegantly synthesize such compounds (*e.g.*, triptolide and tripdiolide) with a fused highly-functionalized tetracyclic skeleton bearing multiple chiral centers, as well as their analogs and derivatives, especially on a large scale. For the exploration of elegant chemical processes for triptolides as well as their further biological investigation, we devoted our efforts to the asymmetric synthesis of (–)-triptolide and its analogs, and successfully developed a new approach to (–)-triptolide and its analogs using asymmetric Robinson annulation, Pd(II)-catalyzed lactonization and Friedel–Crafts alkylation as key steps. Herein, we report our preliminary results on this aspect.

Our study was mainly focused on the issue of access to the key compound **4**,[9b,10c,11] which was previously used as a useful building block for the synthesis of (–)-triptolide and (–)-triptonide (Fig. 1). In fact, the construction of the compound not

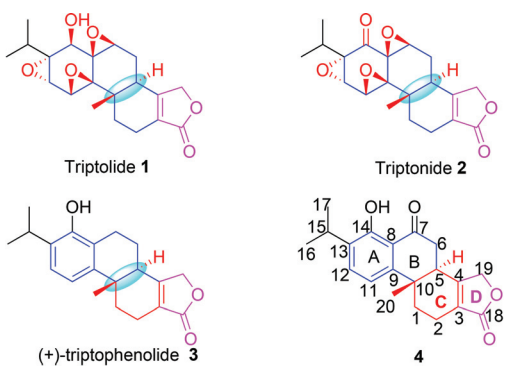

Fig. 1 (–)-Triptolide, (–)-triptonide, and their known intermediate **4**.

[a]*State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, Gansu 730000, P. R. China. E-mail: tangyu@lzu.edu.cn, liying@lzu.edu.cn; Fax: +86 (931)8912582*
[b]*Gansu Institute for Chemical Industry, 1st Guchengping, Lanzhou, Gansu 730000, P. R. China*

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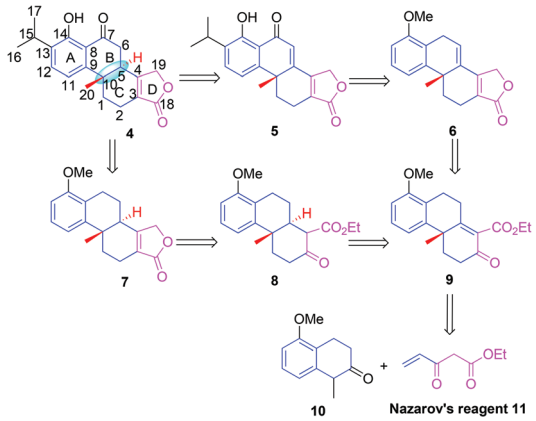
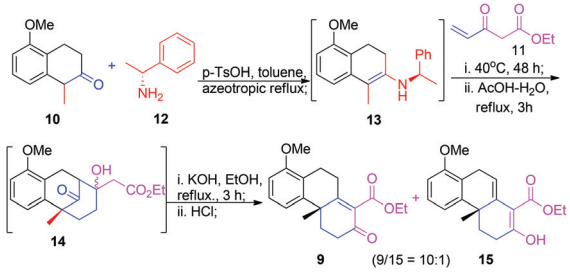


Scheme 1 Retrosynthetic analysis of **4**.

only gave the skeleton of the natural products, but also provided the chiral source for all other chiral centers in natural products, and the chiral centers at 5- and 10-position will induce the formation of chiral centers at 7-, 8-, 9- and 11-, 12-, 13-, 14-position of triptolide, so clearly the efficient asymmetric construction of the fused tetracyclic ring system presents a major synthetic challenge. As our retrosynthetic analysis outlined in Scheme 1, the lactone ring D could be assembled by Pd(II)-catalyzed carbonylation–lactonization, and the ring C with the first chiral center at 10-position could be conceived by asymmetric Robinson annulations of Nazarov's reagent **11**[13] and the commercially available ketone **10** with the pre-installed ring A/B. The stereogenic center at 5-position of the synthon **4** could be introduced by stereoselective hydrogenation induced by the pre-constructed chiral center at 10-position, and the isopropyl group in ring A could be assembled by Friedel–Craft alkylation of the compound **6** or **7**.

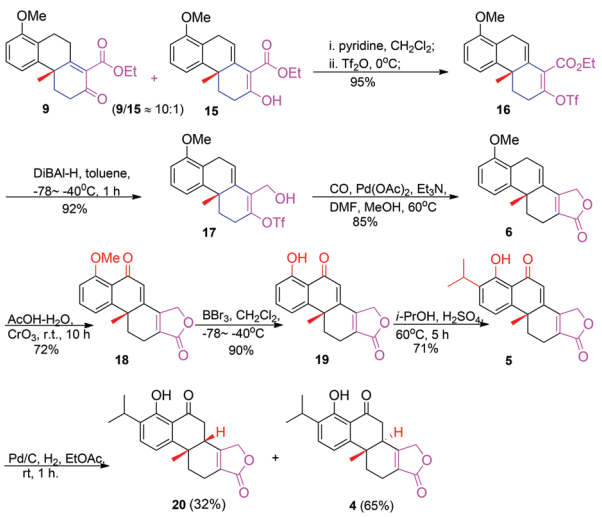
According to the above synthetic consideration, as shown in Scheme 2, our synthesis began with the asymmetric construction of the ring C. Based on the two-step enantioselective synthesis of tricyclic enones reported by Spencer and co-workers in 2006,[8a] the Robinson annulation of compounds **10** and **11** was selected as a key step for this purpose. Interestingly, simple enantiomerically pure α-phenylethylamine has been used by d'Angelo and co-workers[15] to effect enantioselective Michael additions. Inspired by the success of such an auxiliary in the asymmetric Robinson annulation of Nazarov's reagent **11** with 2,5,5-trimethylcyclohexanone,[16] the chiral amine was



Scheme 2 Construction of ring C.

then utilized to effect asymmetric Robinson annulation of **10** and **11** to form the tricyclic compound **9**. According to the literature,[16,17] 5-methoxy-2-tetralone (**10**) reacted with (*R*)-(+)-α-phenylethylamine (**12**) in the presence of *p*-toluenesulfonic acid under azeotropic reflux to afford the enamine **13**, which reacted *in situ* with Nazarov's reagent **11**[13a] to yield the bridged intermediate **14** along with traces of compound **9** after hydrolysis in aqueous acid. Treatment of the crude mixture of **14** and **9** with potassium hydroxide afforded the desired annulation product **9** along with its enol isomer **15**. The total yield of **9** and **15** was 62% from the starting compound **10**. The ratio of products **9** and **15** is about 10 : 1. They could be separated by column chromatography to give the isomerically pure **9** and the less stable **15**. The enantiomeric excess of **9** was 90% as determined by the HPLC analysis. The structural spectroscopic data of **9** are consistent with those of the structurally analogous tricyclic enones containing angular methyl groups.[14,17,18]

After the completion of C-ring construction, we then focused on constructing the lactone ring D. In terms of the Pd-catalyzed carbonyl-insertion reaction of vinyl triflate reported by Crisp in 1992,[19] a Pd(II)-catalyzed carbonylation–lactonization sequence was designed for the construction of ring D (Scheme 3). A mixture of **9** and **15** was treated with triflic anhydride and pyridine in dichloromethane. Vinyl triflate **16** was formed in 95% yield. Then, the screening was focused on the conditions for reducing **16** to **17**. With failed attempts using $LiAlH_4$, $NaBH_4/I_2$ and $NaBH_4$/Lewis acid as reducing reagents, pleasingly compound **16** was readily reduced with diisobutylaluminum hydride (DiBAl-H) in toluene from −78 to −40 °C to yield the allylic alcohol **17** in 92% yield. With compound **17** in hand, the key palladium-catalyzed carbonylation[20] was then performed in the presence of carbon monoxide, giving the lactone **6** with the newly formed ring D in 85% yield with 98% ee after crystallization. Notably, compared with the previous use of $Pd(PPh_3)_4$ as a catalyst in similar procedures reported by Yang[21] and Mikulas,[22] the cheap and air-stable $Pd(OAc)_2$ as a



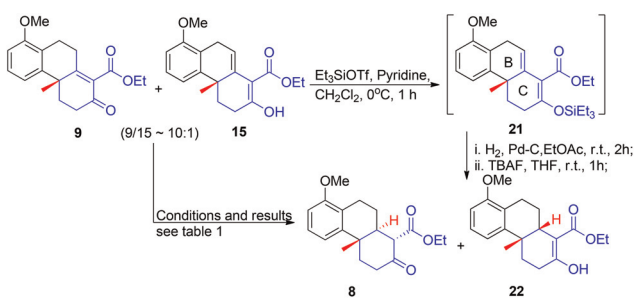
Scheme 3 The synthesis of **4**.

catalyst[23] was found to be effective in this titled carbonylation–lactonization.

The next step is to introduce an isopropyl group on ring A (Scheme 3). Due to the presence of the methoxyl group on ring A, the activity of ring A for electrophilic substitution is increased and would greatly facilitate its Friedel–Crafts alkylation. However, surprisingly the model reactions using 2-methoxyacetophenone and 2-hydroxyacetophenone demonstrated that the presence of the phenolic hydroxyl group was definitely important in such an electrophilic substitution. In contrast to the less reactivity of 2-methoxyacetophenone in the Friedel–Crafts alkylation, 2-hydroxy-acetophenone as a substrate could smoothly undergo the titled alkylation in the presence of isopropanol in concentrated sulfuric acid. In addition, considering the potential competition of benzylic oxidation, it is necessary to introduce the carbonyl group at the benzylic position of ring B before installing the isopropyl group at ring A. Based on the above facts and considerations, treatment of **6** with CrO_3 in AcOH–H_2O (9 : 1) was firstly conducted, producing the desired enone **18** in 72% yield. The crude product **18**, used directly in the next step without purification, was demethylated with BBr_3 in CH_2Cl_2 to yield **19** in 90% yield. Recrystallization of **19** gave the white crystal with 98% ee, and its structure was further confirmed by X-ray crystallographic analysis. Then, the site-selective Friedel–Crafts alkylation of the phenol **19** proceeded in concentrated sulfuric acid in the presence of isopropanol at 60 °C, affording the alkylated product **5** in 71% yield with 99% ee after recrystallization.

For the synthesis of **4**, the final challenge is the stereoselective reduction of the double bond in **5** to construct the crucial chiral center at the 5-position (Scheme 3). The direct hydrogenation of **5** catalyzed by 5% Pd-C yielded two diastereoisomers **4** and **20** with a 2 : 1 dr in a combined yield of 97%. Unfortunately, these isomers could not be chromatographically separated. Gratifyingly, one recrystallization of the above mixture from CH_2Cl_2–Et_2O could partially give the desired isomerically pure **4** with more than 99% ee, but this was not the case for its epimer **20**.

To further improve the synthetic efficiency, a modification focused on the construction of the C-5 chiral center was then pursued. As shown in Scheme 4, the initial conversion of a mixture of **9** and **15** was mainly attempted to directly yield the ketoester **8**. The preliminary results are shown in Table 1.



Scheme 4 Synthesis of intermediate **8** using an alternative method to form **4**.

Table 1 Direct reduction trials of **9** and **15** to yield **8**

Entry	Conditions	Results (isolated yields)
1	$Pd/BaSO_4$, H_2, MeOH	**8** (15%) + **22** (60%)
2	Li/NH_3(l), *t*-BuOH, THF	Decomposed
3	Li/NH_3(l), *t*-BuOH, Et_2O	**8** (67%) + **22** (15%)

When a mixture of **9** and **15** (*ca.* 10 : 1 dr) was subjected to the reduction with $Pd/BaSO_4/H_2$, the undesired product **22** was mainly yielded (entry 1, Table 1). The reduction with Li/NH_3/*t*-BuOH in THF resulted in the decomposition of **9** and **15** (entry 2, Table 1). Interestingly, however, the related reduction in diethyl ether as a solvent could afford the desired product **8** in 67% yield, together with **22** in 15% yield (entry 3, Table 1). Despite a better diastereoselectivity obtained in this case than that observed in the above reduction of **5** to **4** (Scheme 3), the result for the target-oriented synthesis was still not satisfactory. Therefore, an indirect approach was further tested.[24] A mixture of **9** and **15** (*ca.* 10 : 1 dr) was converted to silyl ether **21** by treatment with triethylsilyl triflate and pyridine; subsequent Pd-C catalyzed hydrogenation and tetrabutylammonium fluoride (TBAF)-mediated desilylation of **21** yielded the desired product **8** in 83% yield over three steps along with a trace amount of **22**. After recrystallization from CH_2Cl_2–Et_2O, the diastereomerically pure **8** with 98% ee was obtained. The structures of **8** and **22** were initially assigned by comparing their spectra with similar compounds reported by Yang's group,[11c] and finally confirmed by X-ray crystallographic analysis of **8**.

X-ray data of structures **8** and **19** have been deposited in the Cambridge Crystallographic Data Centre: CCDC 931770 and CCDC 926225, respectively.

Compared with the enone **9**, the silyl dienol ether **21** having two conjugated double bonds formed a more planar structure, which increased the dihedral angle between ring B and ring C of **21** (Fig. 2). Such a conjugated diene structure made it easier for the hydrogenation of the C-5 double bond from the opposite direction of C-10 methyl to yield the desired compound **8** with improved diastereoselectivity.

Using **8** as the key intermediate, the synthesis of **4** was executed similarly to the preparation of **5** from **9** and **15** (Scheme 3). As shown in Scheme 5, treatment of **8** with potassium hexamethyldisilazane followed by *N*-phenyl bis(trifluorosulfonyl)imide ($PhNTf_2$) in tetrahydrofuran (THF) yielded the triflate **23** in 93% yield.[25] Then, the reduction of **23** with

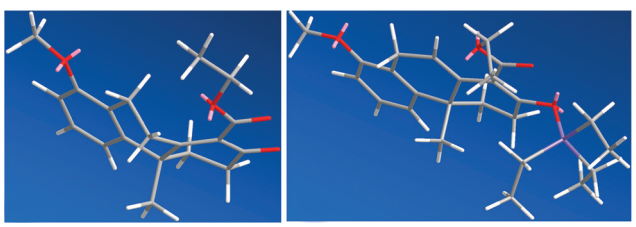
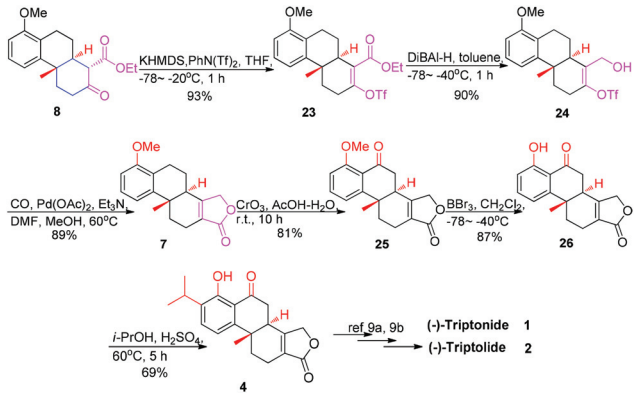


Fig. 2 The 3-D structure of compounds **15** and **21**.



Scheme 5 Modified synthesis of **4**, (–)-triptonide, and (–)-triptonide.

DiBAl-H in toluene gave the allylic alcohol **24** in 90% yield. The subsequent carbonylation–lactonization sequence catalyzed by $Pd(OAc)_2$ converted **24** to the intermediate **7** in 89% yield with 98% ee. Oxidation of **7** with CrO_3 in aqueous acetic acid (90% v/v) yielded **25** in 81% yield. The compound **25** was then demethylated with BBr_3 in CH_2Cl_2 at −78 °C to form the phenol **26** in 87% yield. Finally, the Friedel–Crafts isopropylation of **26** with isopropanol in sulfuric acid afforded the desired product **4** in 69% yield. After recrystallization, the enantiopure compound **4** was obtained with more than 99% ee.

Presently, our novel synthesis of **4** is accomplished with more 99% ee and excellent disastereoselectivities in 9 steps with 13.6% total yield and 11 steps with 18.5% overall yield through two synthetic schemes. With the compound **4** in hand, (–)-triptonide (**2**) and (–)-triptolide (**1**) could be rapidly synthesized according to the previously reported stategies.[11a,b]

Conclusions

In summary, a novel formal synthesis of (–)-triptolide and (–)-triptonide has been achieved based on the alternative enantioselective synthesis of the known key building block **4** using a chiral amine-mediated asymmetric Robinson annulation, stereoselective hydrogenation controlled by a chiral substrate, Pd(II)-catalyzed carbonylation–lactonization and Friedel–Crafts isopropylation as the key steps. The current synthesis gave a good overall yield and high enantio- and diastereo-selectivity, resulting in an efficient, elegant, and scalable synthesis of triptolides. This work also provided a new useful approach to the synthesis of other structurally relevant natural products or bioactive derivatives. Further synthetic and biological investigations in this field are currently underway in our laboratory.

Acknowledgements

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25 The investigation has also found that **8** cannot be converted to **23** under the treatment of triflic anhydride (Tf_2O)/pyridine and the reaction of **8** with Tf_2O in the presence of NaH in tetrahydrofuran gave a 90% yield of **23** along with a lot of polymer formed from the Tf_2O-catalyzed polymerization of THF.

