OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Asymmetric Total Synthesis of TAN-1085 Facilitated by Pd-Catalyzed Atroposelective C−H Olefination

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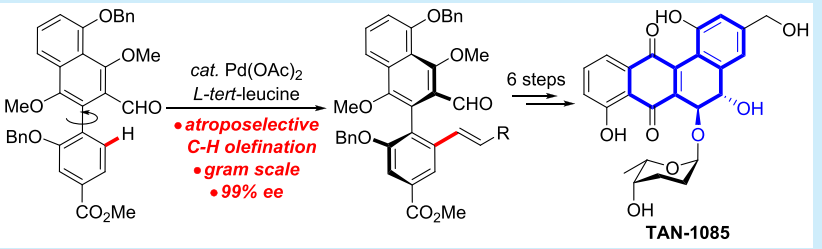
Supporting Information



ABSTRACT: Asymmetric total synthesis of TAN-1085 via Pd-catalyzed atroposelective C−H olefination is described. This synthesis features the gram-scale construction of axially chiral biaryls in an enantiopure form employing the readily available L-*tert*-leucine as the chiral transient auxiliary. The synthetic approach might provide a unified strategy for the total synthesis of natural products containing *trans*-9,10-dihydrophenanthrene-9,10-diol motifs.

The *trans*-9,10-dihydrophenanthrene-9,10-diol scaffold (**I**) is the core structural subunit of a wide range of biologically active natural products, such as the anticancer angucycline PD 116740 and TAN-1085,[1a,b] the cytotoxic antibiotic FD 594,[1c,d] and the benanimicin and pradimicin antibiotics (BPAs) (Scheme 1a).[1e−h] The significant biological activity of these natural products as well as their unique molecular architecture have triggered a number of synthetic studies.[2−6] The stereoselective and efficient construction of the core structure of 9,10-dihydrophenanthrene with *trans*-vicinal hydroxyl groups is particularly challenging and has been a central topic of these synthetic efforts. In the seminal work by Suzuki,[3−6] a modified pinacol coupling that stereospecifically transfers the biaryl axial chirality (**II**) to the pseudo-C_2-symmetric trans diols (**I**) was elegantly established as the key step (Scheme 1a).[3] Thereby, the synthetic challenge shifted to the stereoselective synthesis of the axially chiral biaryldialdehydes (**II**), and several strategies were developed (Scheme 1b): (a) a stereochemical-relay strategy involving two chirality transfer steps (central-to-axial and then axial-to-axial) for the synthesis of TAN-1085;[4b] (b) the Bringmann-type asymmetric ring-opening reaction of the biaryl lactone with a chiral nucleophile for the construction of the FD-594 aglycon;[5b,7a,b] and (c) the introduction of a chiral auxiliary to enable an optical resolution via chromatographic separation of the resulting diastereomers for pradimicinone.[6] However, these previous endeavors suffered from the use of stoichiometric chiral reagents, lengthy steps, and/or poor stereocontrol. We envisioned that the development of a general method to efficiently and stereoselectively construct the axially chiral biaryldialdehydes followed by pinacol cyclization would provide a unified strategy to greatly facilitate the total synthesis of these natural products. Undoubtedly, such a unified strategy would offer a great opportunity to access related compounds and elucidate their biological activities.

In recent years, great efforts have been expanded to the asymmetric synthesis of axially chiral biaryl skeletons.[7,8] In particular, asymmetric C−H activation has emerged as a powerful tool to access the axial chirality.[9,10] Recently, a pioneering work of Pd-catalyzed enantioselective C(sp^3)−H functionalization to create point chirality by the use of *tert*-leucine (Tle) as a transient directing group was developed by the Yu group.[10] Inspired by these elegant workd, we applied this strategy to the highly atroposelective synthesis of axially chiral biaryl aldehydes via asymmetric C−H functionalizations.[11] We speculated that our previously developed Pd-catalyzed atroposelective C−H olefination could streamline the synthesis of *trans*-9,10-dihydrophenanthrene-9,10-diol[11a] since the resulting olefins can be easily transferred to aldehydes. Notably, despite the significant advance as well as the promising prospect of enantioselective C−H activation in organic synthesis,[9] examples of using the enantioselective C−H activation strategy to expedite the synthesis of natural products were still rare.[12−14] As part of our persistent pursuit to promote concise synthesis of natural products via C−H activation,[11b] herein, we report a novel approach that enables the asymmetric total synthesis of TAN-1085 based on palladium-catalyzed asymmetric C−H olefination (Scheme 1c).

Our retrosynthetic analysis for TAN-1085 is shown in Scheme 2. The axially chiral biaryldialdehyde **1** would be the crucial precursor for TAN-1085, which would undergo pinacol

Received: March 28, 2019

DOI: 10.1021/acs.orglett.9b01099
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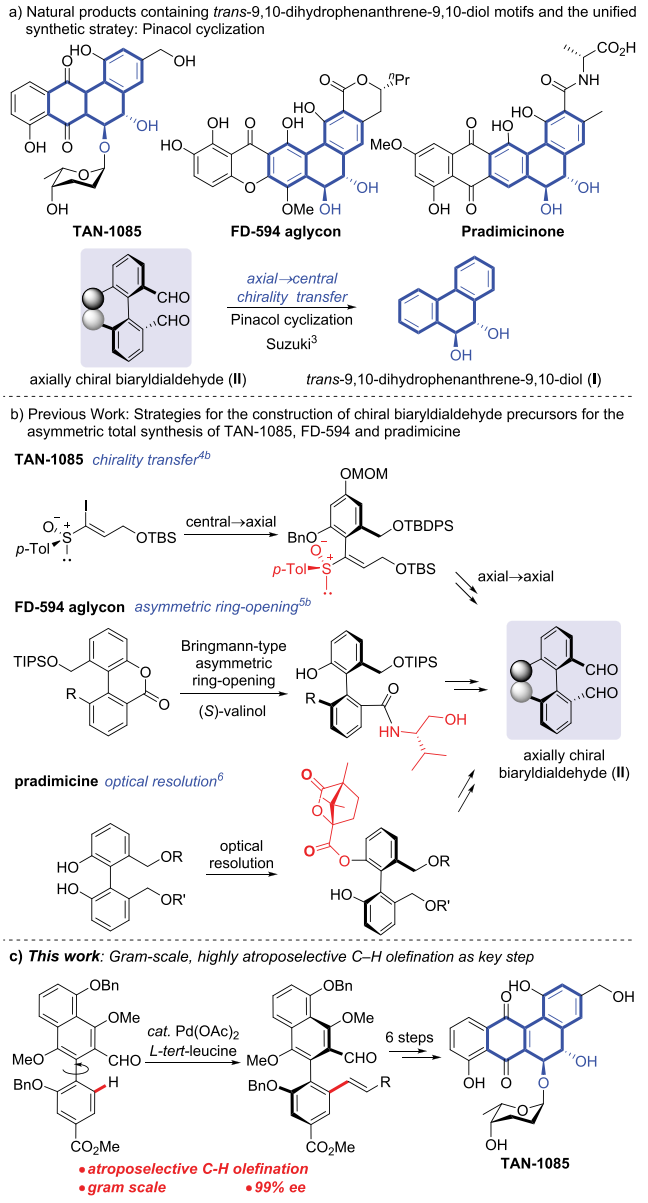
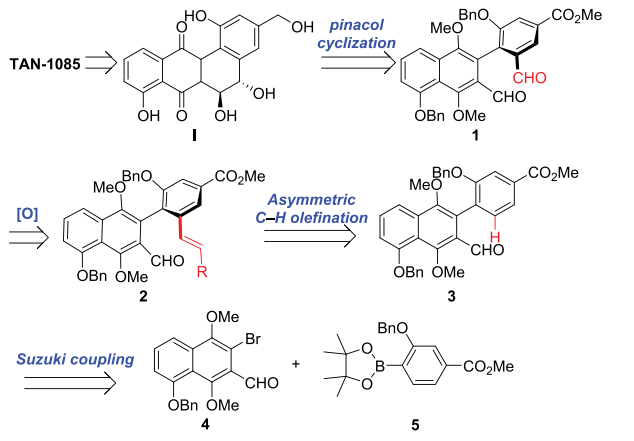
Scheme 1. Natural Products Containing *trans*-9,10-Dihydrophenanthrene-9,10-diol Motifs and the Synthetic Strategies



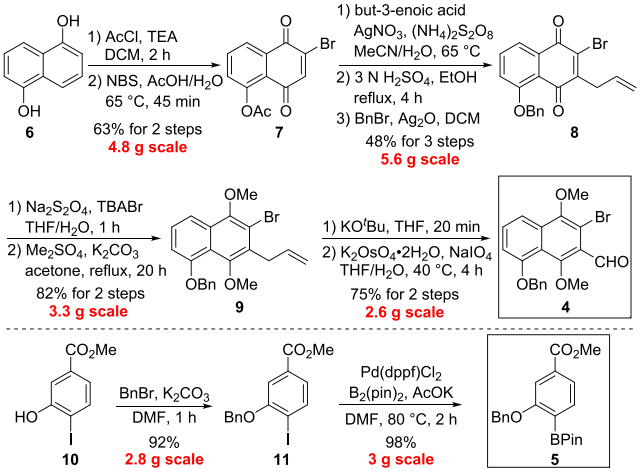
Scheme 2. Retrosynthetic Analysis for TAN-1085



cyclization to form diol **I** stereoselectively.[3−6] The formyl group could be generated by oxidative cleavage of the double bond in **2**, which would be obtained via Pd-catalyzed atroposelective C−H olefination of **3**.[11a] **3** could be easily accessed by Suzuki coupling of **4** and **5**. Though promising as it seemed, the direct subjection of **3** to the atroposelective C−H olefination might be encountered with several challenges: (i) the substrate **3** used in this reaction is extremely electron-rich, and its compatibility with the oxidative conditions would be a potential challenge; (ii) the vicinal methoxy group coupled with the *in situ* formed imine group and the carboxylate of Tle might act as a tridentate chelating group, which might deactivate the palladium catalyst; (iii) whether benzyloxy and methoxy substituents are sterically bulky enough to prevent rotation about the biaryl axis;[15] (iv) the scalability (gram scale) of this reaction for further transformations would be another challenge.

Our synthesis commenced with the preparation of building blocks **4** and **5** (Scheme 3). A modified procedure was

Scheme 3. Syntheses of Fragments 4 and 5



developed for the preparation of compound **4** with high efficiency and simplified operations on a multigram scale.[16] Acetate protection of the free phenolic hydroxyl group of commercially available **6**, followed by treatment with *N*-bromosuccinimide, afforded **7** in 63% yield upon recrystallization.[17] Allylation of **7** with but-3-enoic acid in the presence of $(NH_4)_2S_2O_8$ and catalytic amount of $AgNO_3$[16] and subsequent deacylation and benzylation provided **8** in a 48% overall yield for 3 steps on a 5.6 g scale. Napthoquinone **8** was transferred to its dimethoxy benzyl form **9** in 82% yield. **9** was then converted to the bromo-aldehyde **4** in 75% yield for 2 steps on a 2.6 g scale.[16] Overall, the coupling partner **4** was prepared in a total yield of 19% over 9 steps on a multigram scale with one recrystallization and three chromatography operations. Then, we set out to prepare fragment **5** for Suzuki coupling. A bismethoxymethyl (MOM) protected phenol was used in the first total synthesis of TAN-1085 developed by Suzuki, and subsequent three-step transformation of the MOM ether to CO_2 Me was needed, due to the incompatibility of CO_2 Me with the reaction conditions.[4] Considering the mild reaction conditions of our route, we decided to introduce CO_2 Me at the beginning to simplify the synthesis. Benzyl protection of the phenolic hydroxyl of **10**, followed by borylation under Miyaura coupling conditions,[18] afforded **5** in excellent yield.

DOI: 10.1021/acs.orglett.9b01099
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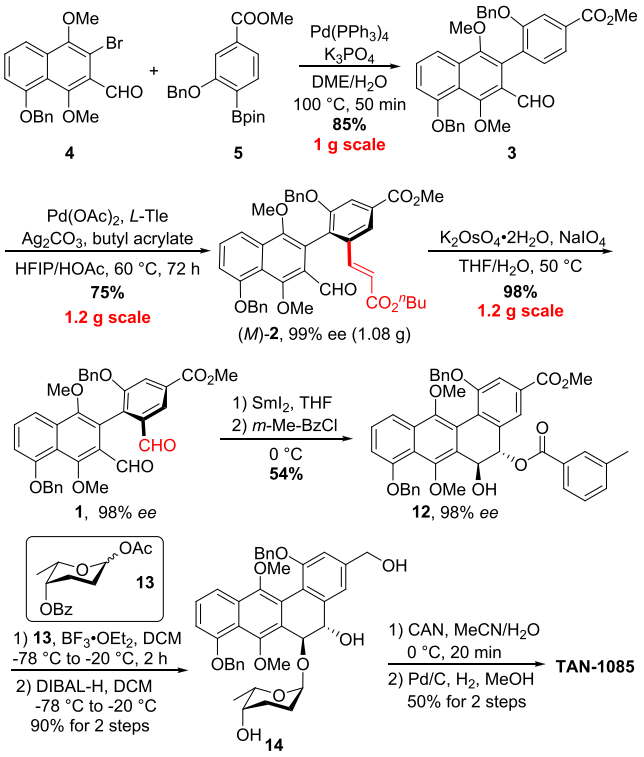
The sugar motif **13** was prepared according to literature procedure.[4,19]

Suzuki coupling between **4** and **5** led to the formation of the desired racemic biaryl **3** in 85% yield on a 1 g scale (Scheme 4). The reaction was better conducted in a sealed tube, and the

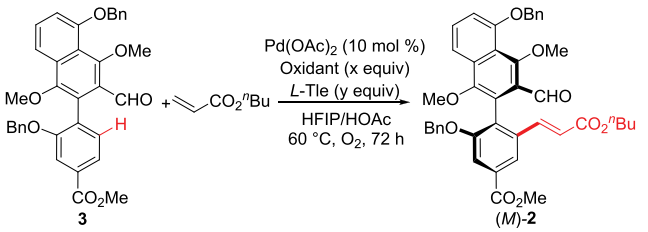
Scheme 4. Asymmetric Total Synthesis of TAN-1085



reaction under reflux resulted in relatively lower yield. Then, we focused our attention on the asymmetric C−H olefination of **3**. At the outset, **3** was directly subjected to our previously reported conditions, that is $Pd(OAc)_2$ (10 mol %), BQ (0.1 equiv), and L-Tle (0.2 equiv) in HFIP/HOAc (0.5 mL) at 60 °C under O_2 for 72 h. However, (*M*)-**2** was obtained in only 31% yield with 90% ee (Table 1, entry 1).[20] Despite that an unsatisfactory yield and ee were obtained, the reaction system was relatively clean, and most unreacted starting material **3** could be recovered, indicating the robustness of **3** under the oxidative and acidic conditions. Further optimization showed that the equivalent of L-Tle was crucial for the enantioselectivity, and the ee value was elevated to >99% when using 40 mol % of L-Tle (entry 2). Increasing the amount of BQ only resulted in a little bit of improved yield (entry 3). Then we screened different Ag salts as oxidants. Gratifyingly, when 4 equiv of Ag_2CO_3 was used, the reaction could be conducted on a 1.2 g scale, and the desired product (*M*)-**2** could be obtained in 75% isolated yield with 99% ee (entry 9, (*M*)-**2**, 1.08 g).[21]

With gram-scale enantiopure **3** in hand, our attention was turned to the oxidative cleavage of the double bond. Elevated temperature and extended reaction time were required for the complete conversion, and portionwise addition of K_2OsO_4 and $NaIO_4$ under 50 °C enabled the preparation of biaryldialdehyde **1** in high yield and ee (98%, 98% ee, 1.03 g). Hitherto, we have succeeded in the gram-scale preparation of the key axially chiral biaryldialdehyde precursor of TAN-1085 with 98% ee. Subsequently, treatment of **1** with SmI_2, followed by *in*

Table 1. Asymmetric C−H Olefination of 3[a]



entry	oxidant (*x* equiv)	L-Tle (*y* equiv)	yield (%)[b]	ee (%)[c]
1	BQ (0.1)	0.2	30	90
2	BQ (0.2)	0.4	41	>99
3	BQ (1)	0.4	47	>99
4[d]	AgOAc (4)	0.4	46	>99
5[d]	AgOAc (6)	0.4	44	>99
6[d]	Ag_3PO_4 (1.3)	0.4	35	>99
7[d]	Ag_2SO_4 (2)	0.4	34	>99
8[d]	Ag_2CO_3 (2)	0.4	51	>99
9[d,e]	Ag_2CO_3 (4)	0.4	75	99

[a]Reaction conditions: **3** (0.05 mmol), butyl acrylate (4.0 equiv), $Pd(OAc)_2$ (10 mol %), oxidant (*x* equiv), and L-Tle (*y* equiv) in HFIP/HOAc (0.5 mL) at 60 °C under O_2 for 72 h. [b]Isolated yield. [c]The ee value was determined by HPLC. [d]N_2 instead of O_2. [e]**3** (1.2 g, 2.1 mmol) was used.

situ monoprotection with 3-methylbenzoyl chloride, gave **12** in 54% yield over two steps.[4] Finally, TAN-1085 was obtained in enantio- and diastereomerically pure form after glycosylation and deprotection.[4] The spectroscopic data of TAN-1085 were in good agreement with that reported by Suzuki et al.[4b]

In conclusion, a concise total synthesis of TAN-1085 has been achieved in 17 linear steps with 3% overall yield. The route features a scalable, atroposelective axial-chirality construction as a key step via Pd-catalyzed asymmetric C−H olefination, which employs commercially available L-Tle as an inexpensive, catalytic transient chiral auxiliary. We believe this asymmetric synthetic strategy would serve as a unified strategy to facilitate the total synthesis of other natural products containing *trans*-9,10-dihydrophenanthrene-9,10-diol motifs, and related works are currently underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01099.

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

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.9b01099
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■ ACKNOWLEDGMENTS

Financial support from the NSFC (21572201, 21772170), the National Basic Research Program of China (2015CB856600), the Fundamental Research Funds for the Central Universities (2018XZZX001-02), and Zhejiang Provincial NSFC (LR17B020001) is gratefully acknowledged.

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(20) The absolute configuration of compound **2** was deduced from previous studies (ref 11a) and confirmed by the optical rotation and NMR spectra of the final product TAN-1085 (ref 4b).

(21) Consistent with our previous results (ref 11a) and Sternhell's investigations (ref 15), alkoxy groups are generally less sterically bulky; therefore, *rac*-**3** could undergo the atroposelective C−H olefination through dynamic kinetic resolution.

DOI: 10.1021/acs.orglett.9b01099
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