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Asymmetric Total Synthesis of PD-116740

Chaoying Zheng, Tao Xie, Haibing He,* and Shuanhu Gao*

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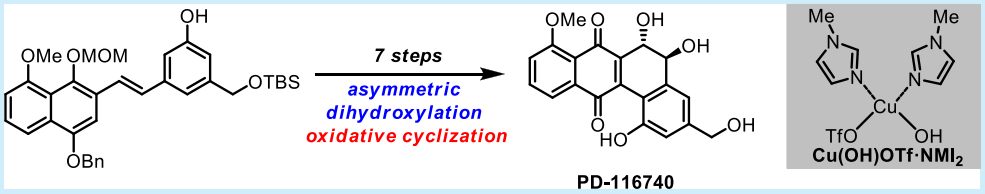

ABSTRACT: A new approach was developed to achieve the asymmetric total synthesis of (+)-PD-116740, an angucyclinone from the actinomycete isolate (WP 4669). A sequence of asymmetric dihydroxylation followed by oxidative cyclization was applied to stereoselectively construct the core *trans*-9,10-dihydrophenanthrene-9,10-diol B−C−D ring. A new Cu salt Cu(OH)OTf·NMI_2 was found to be the best oxidant to induce the oxidative coupling and phenol oxidation.

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In 1985, Hokanson and co-workers reported the discovery of PD-116740 (**1**) from fermentation broth of the actinomycete isolate (WP 4669) (Figure 1).[1] It belongs to a big family of angucycline polycyclic aromatic polyketides,[2] and exhibits activities against HCT-8 human adenocarcinoma (IC_{50} = 3.3 μm) and LI210 lymphocytic leukemia (IC_{50} = 2.1 μm). PD-116740 contains a highly oxygenated angular tetracyclic skeleton including a *trans*-9,10-dihydrophenanthrene-9,10-diol fragment (B−C−D ring), which is distinguished with the most commonly occurring fully aromatized angucycline antibiotics. The same biosynthetic pathway[3] leads to the formation of biogenetically and structurally related polycyclic polyketides including PM070747 (**2**)[4] TAN-1084 (**3**)[5] and TAN-1085 (**4**). The structural unit of *trans*-dihydrophenanthrene-diol also exists in the xanthone-type natural product FD-594 aglycon (**5**).[6]

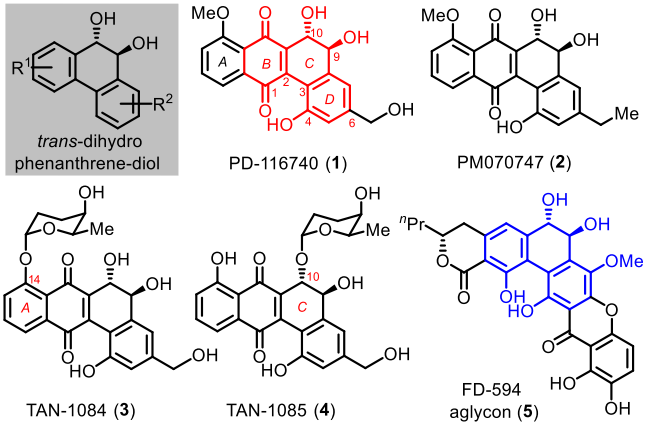

Figure 1. *trans*-9,10-Dihydrophenanthrene-9,10-diol-containing natural products.

The intriguing structures and promising biological activities of these polyketides have led many groups to develop syntheses, including the Larsen,[7] Hauser,[8] Suzuki,[9] and Shi[10] groups. In 2008, Suzuki and co-workers took advantage of a strategy of chirality transfer from axial to central and SmI_2-mediated Pinacol cyclization to build the *trans*-9,10-dihydrophenanthrene-9,10-diol, which was used in the first total synthesis and absolute structure assignment of **1** (Scheme 1A).[9] This strategy was also successfully used in the asymmetric synthesis of TAN-1085 (**4**) and FD-594 aglycon (**5**) by the same group.[11] Shi and co-workers developed a Pd-catalyzed atroposelective C−H olefination to construct the axially chiral biaryls, which was used in the total synthesis of TAN-1085 (**4**) (Scheme 1B).[10] Recently, we developed a new strategy involving an asymmetric dihydroxylation and a Cu-mediated oxidative phenol coupling reaction to build the *trans*-dihydrophenanthrenediol fragment which was used in the total synthesis of FD-594 (Scheme 1C).[12] As a further application of this strategy, we reinvestigated the Cu-promoted oxidative cyclization and achieved the asymmetric total synthesis of (+)-PD-116740.

Taking advantage of the convergent approach, we first planned to prepare A/B and D ring fragments (Scheme 2). Commercially available naphthalene-1,5-diol was selected as the starting material, which could be transformed into quinone **12** and **12′** through a known procedure on a large scale (Scheme 2A).[13] Reduction of quinone by sodium hydrosulfite

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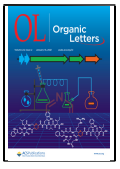

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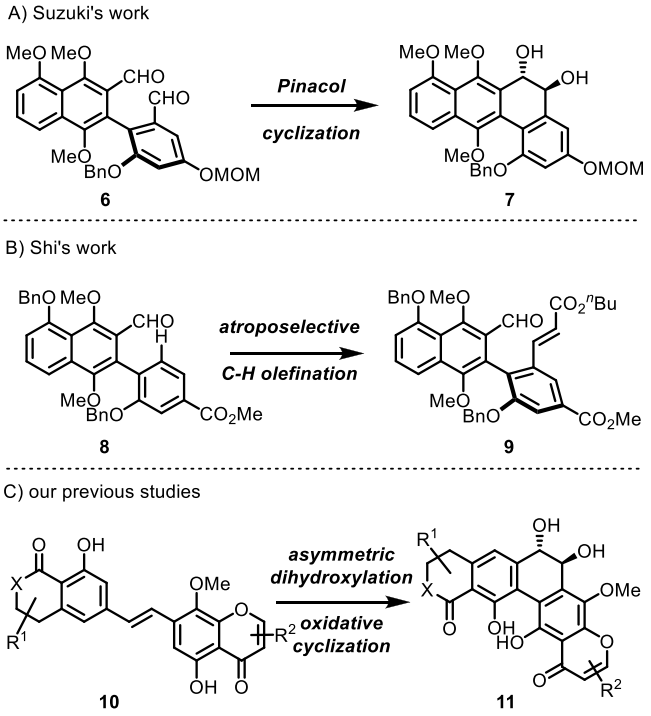
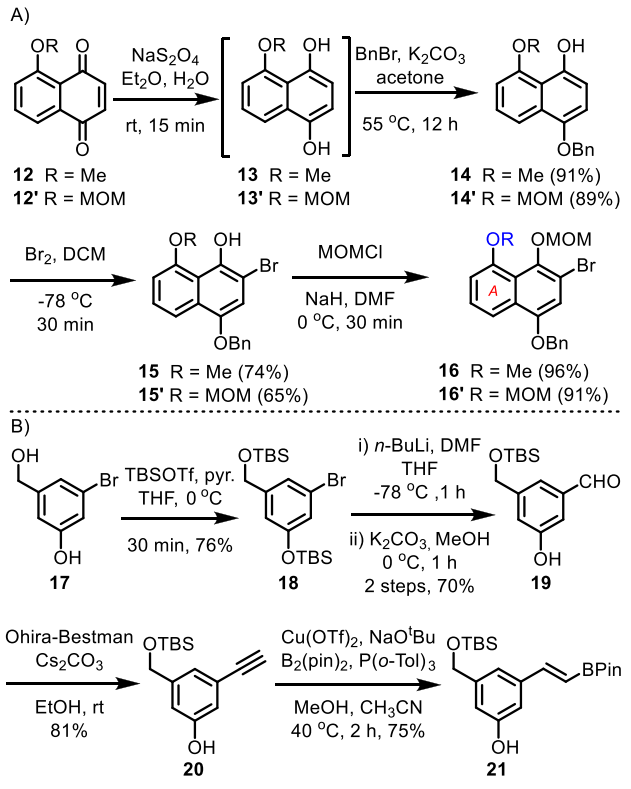
Scheme 1. Strategies for the Construction of the *trans*-9,10-Dihydrophenanthrene-9,10-diol Framework



Scheme 2. Preparation of A/B and D Ring Fragments



gave hydroquinone, and the less sterically hindered phenol group was protected as the benzyl ether to form the phenol **14** in 91% yield over two steps. After selective bromination at the ortho-position[14] (74%) and MOM protection (96%) of the last phenol group, fragment **16** was achieved as the precursor of the coupling reaction. Using the same procedure, quinone **12′** was converted to **16′** in 53% total yield over four steps on a decagram scale. Compounds **16** and **16′** containing an A−B ring with different protecting groups might facilitate the selective deprotection and preparation of derivatives.

The preparation of the D ring fragment commenced with the known benzyl alcohol **17** (Scheme 2B).[15] TBS protection of the diol provided **18** in 76% yield. Lithium/bromide exchange with *n*-BuLi gave the anion species, which interacted with dimethyl formamide (DMF) to introduce the aldehyde group. After selective deprotection of phenol-TBS group under basic conditions, **19** was generated in 70% over two steps. The aldehyde was then converted into alkyne with dimethyl 1-diazoacetonylphosphonate (Ohira−Bestmann reagent)[16] to afford **20**. The terminal alkyne was then subjected to Cu-catalyzed vinyl boration conditions[17] to give compound **21** in 75% yield as another coupling fragment.

With both A/B and D rings in hand, a Pd-catalyzed Suzuki−Miyama reaction[18] was utilized for the coupling of two fragments (Scheme 3). Treatment of **16** or **16′** and **21** with $Pd(dppf)Cl_2$·DCM in the presence of K_2CO_3 in *t*-BuOH and

Scheme 3. Total Synthesis of PD-116740

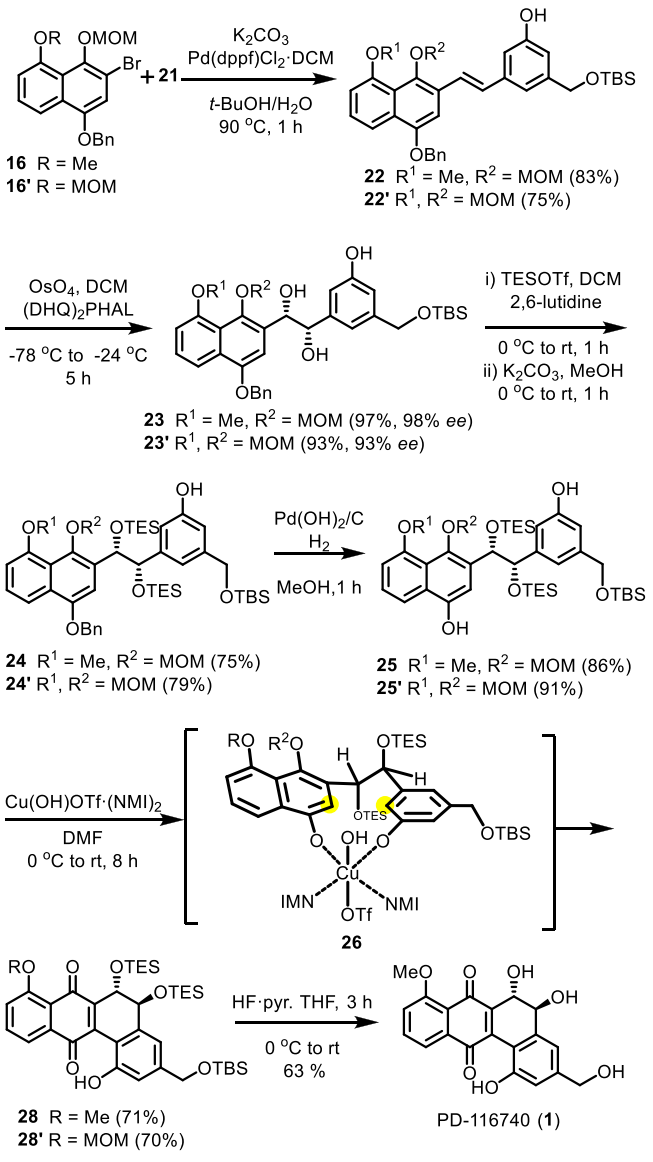


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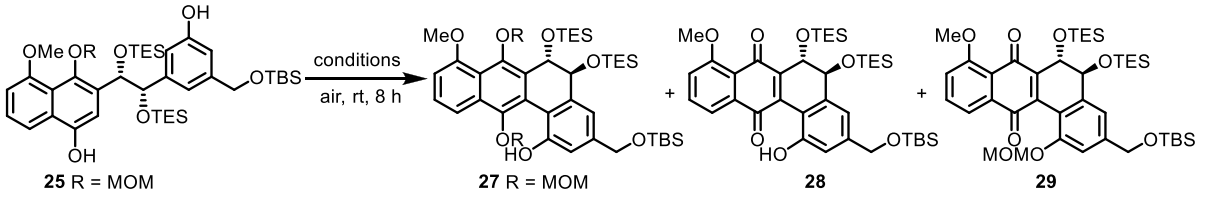
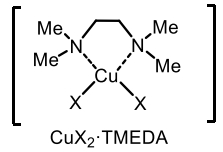
Table 1. Optimization Conditions of Cu-Mediated Oxidative Coupling

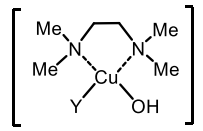


25 R = MOM **27** R = MOM **28** **29**

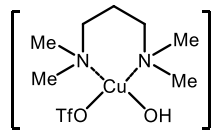
entry[a]	oxidant	solvent[b]	conversion	result	
				27:28:29	Yield of **28**[c]
1	$CuCl_2$+TMEDA (2.0 equiv.)	CH_3CN	100%	1:7:1	29%
2	$Cu(OTf)_2$+TMEDA (2.0 equiv.)	CH_3CN	100%	0:1:0	11%
3	Cu(OH)Cl·TMEDA (2.0 equiv.)	CH_3CN	100%	1:3:1	32%
4	Cu(OH)Cl·TMEDA (1.0 equiv.)	CH_3CN	100%	1:3:1	32%
5	Cu(OH)Cl·TMEDA (0.5 equiv.)	CH_3CN	100%	1:3:1	32%
6	Cu(OH)Cl·TMEDA (0.1 equiv.)	CH_3CN	86%	2:2:1	10%
7	Cu(OH)Br·TMEDA (0.5 equiv.)	CH_3CN	100%	1:3:1	18%
8	Cu(OH)OTf·TMEDA (0.5 equiv.)	CH_3CN	100%	1:2:1	13%
9	Cu(OH)OTf·TMPDA (0.5 equiv.)	CH_3CN	100%	2:2:1	10%
10	Cu(OH)OTf·NMI_2 (0.5 equiv.)	CH_3CN	100%	0:1:0	48%
11	Cu(OH)OTf·NMI_2 (0.5 equiv.)	THF	45%	1:2:0	13%
12	Cu(OH)OTf·NMI_2 (0.5 equiv.)	DCE	100%	0:1:0	12%
13	Cu(OH)OTf·NMI_2 (0.5 equiv.)	DCM	100%	0:1:0	4%
14	Cu(OH)OTf·NMI_2 (0.5 equiv.)	DMF	100%	0:1:0	74%
15	Cu(OH)Cl·TMEDA (0.5 equiv.)	DMF	100%	1:2:1	31%
16	Cu(OH)OTf·TMEDA (0.5 equiv.)	DMF	83%	0:4:1	20%
17	Cu(OH)OTf·NMI_2 (0.5 equiv.)	DMF	100%	0:1:0	71%[d]



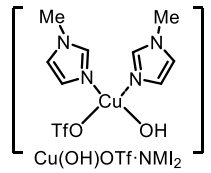
CuX_2·TMEDA



Cu(OH)Y·TMEDA



Cu(OH)OTf·TMPDA



Cu(OH)OTf·NMI_2

[a]Reaction scale: 19 mg. [b]Reaction volume: 1 mL. [c]Determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. [d]Isolated yield.

water produced the desired coupling product **22** and **22′** in 83% and 75% yield, respectively. Asymmetric dihydroxylation of the disubstituted alkene with osmium tetroxide and chiral ligand $(DHQ)_2PHAL$ provided chiral diol **23**[19] in excellent yield of 97% as well as the excellent enantioselectivity of 98% ee (determined by HPLC, see details in the Supporting Information). Another diol **23′** was also afforded with good yield and enantioselectivity (93%, 93% ee). The three hydroxyl groups were then protected by the TES group, and the phenol-TES ether was selectively removed under basic conditions to furnish **24** and **24′** in good yield. It has been proven that the introduction of the bulky TES silyl groups on the diol helps to induce the following oxidative coupling and prevents the oxidative cleavage reaction. Then removal of the benzyl group gave the oxidative coupling precursor **25** and **25′**.

We next turned our attention to construct the *trans*-9,10-dihydrophenanthrene-9,10-diol unit through an oxidative cyclization reaction. The Cu-mediated oxidative coupling has been extensively used in the total synthesis of polyketides and peptides.[20] For instance, Tatsuta and co-workers completed the first total synthesis of TMC-66 by using Cu(OH)Cl·$(NMI)_2$-mediated oxidative coupling,[21] and the same copper salt was also used by Ready and co-workers to forge the core skeleton of kigamicins.[22] Baran and co-workers used $[Cu(MeCN)_4][PF_6]$ as the catalyst and TMEDA as a ligand to synthesize arylomycins and analogues.[23] During our previous synthetic studies of FD-594, we found that the oxidative coupling reaction was highly dependent on the anionic effects, ligands, and the reaction atmosphere. For the specific substrates **25** and **25′**, we preferred a double oxidation: (1) oxidative cyclization to form a C2−C3 aryl−aryl bond and (2) further oxidation of the phenol B ring to quinone. Therefore, it is necessary to screen the reaction conditions with respect to the copper(II) salt and ligands.

Using bisphenol **25** as a model substrate, which was subjected to cyclization reaction under the air atmosphere in the room temperature (Table 1). We first tested the oxidative cyclization with stoichiometric amounts of copper(II) salts (2.0 equiv) using TMEDA (2.0 equiv) as a ligand in acetonitrile (entries 1 and 2), which produced a mixture of cyclized products including MOM-protected product **27**, the desired over oxidized product **28**, and MOM-protected over oxidized product **29**.[24] We reasoned that the Cu-mediated oxidative cyclization occurred and generated cyclized product, which could be further oxidized to quinone **28** under aerobic conditions. The generation of **27** and **29** might be caused by an intermolecular and intramolecular migration process of the MOM group from **28**. Koga's reagent[25] Cu(OH)Cl·TMEDA was investigated from stoichiometric to catalytic (entries 3−6, Table 1), and **28** was obtained in a good yield and ratio in the presence of 0.5 equiv Cu salt (entry 5). To improve the reactivity of the oxidant, we prepared other copper catalysts by changing the anion coordinates and ligands (entries 7−10).[26] We found that using Cu(OH)OTf·NMI_2 as an oxidant formed **28** as a single product in 48% yield (entry 10). We envisioned that the *N*-methylimidazole (NMI)[27] acts as a suitable ligand

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to accelerate the formation of the intermediate **26** (Scheme 3) and following cyclization/oxidation. Finally, after screening the reaction solvents (entries 11−17), it was found that the isolated yield of the reaction was increased to 71% when DMF was used as a solvent (entry 17).

Cu(OH)OTf·NMI_2-mediated oxidative cyclization was also tested using bisphenol **25′** and provided the desired product **28′** in a comparative yield. To finish the total synthesis, global removal of the silyl protecting groups in compound **28** produced PD-116740 (**1**) in 63% yield. ^{1}H and ^{13}C NMR spectra and high-resolution mass spectrometry data for this synthetic compound were fully consistent with those of the natural product (Scheme 3).[1,9]

In conclusion, the asymmetric total synthesis of PD-116740 was accomplished through a convergent approach in 13 steps. This achievement disclosed that the asymmetric dihydroxylation followed by oxidative cyclization is a reliable method to stereoselectively construct the *trans*-9,10-dihydrophenanthrene-9,10-diol fragment. In addition, Cu(OH)OTf·NMI_2 was found to be the best oxidant to induce the oxidative cyclization and phenol oxidation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03990.

Experimental procedures, HPLC spectra for **23** and **23′**, 2D-NMR spectra for **27**, and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**, **14**, **14′**, **15**, **15′**, **16**, **16′**, **18**−**22**, **22′**, **23**, **23′**, **24**, **24′**, **25**, **25′**, **27**, **28**, **28′**, and **28**+**29** (ZIP)

■ AUTHOR INFORMATION

Corresponding Authors

Haibing He − *Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China*; Email: hbhe@chem.ecnu.edu.cn

Shuanhu Gao − *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering and Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China*; orcid.org/0000-0001-6919-4577; Email: shgao@chem.ecnu.edu.cn

Authors

Chaoying Zheng − *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, China*

Tao Xie − *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03990

Notes

The authors declare no competing financial interest.

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