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Graphical Abstract

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Asymmetric Total Synthesis of (+)-Isocryptotanshinone and Formal Synthesis of (-)-Cryptotanshinone

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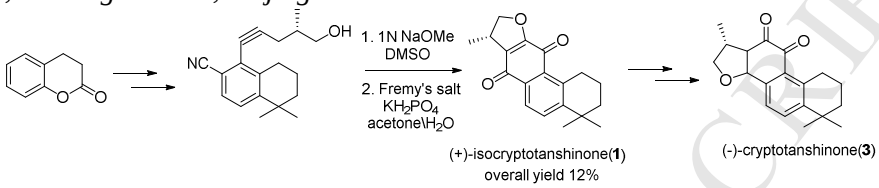
Zhenwei Wang, Xiaozhen Jiao* and Ping Xie*.
No. 2, Nanwei Road, Xicheng District, Beijing



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Asymmetric Total Synthesis of (+)-Isocryptotanshinone and Formal Synthesis of (-)-Cryptotanshinone

Xiang Shi, Xiaoyu Liu, Feilong Yang, Yong Wang, Zhenwei Wang, Xiaozhen Jiao* and Ping Xie*

State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, Beijing Key Laboratory of Active Substances Discovery and Druggability Evaluation, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China.

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ABSTRACT

The first asymmetric total synthesis of (+)-isocryptotanshinone was achieved in 12 linear steps with 12% overall yield from commercially available dihydrobenzopyrone. The key step was a base-mediated cyclization reaction. In addition, the synthetic strategy included the formal synthesis of (-)-cryptotanshinone.

* Corresponding author. E-mail: jiaoxz@imm.ac.cn, xp@imm.ac.cn;
Tel.: +86 10 63165242; fax: +86 10 63017757.

1. Introduction

Salvia miltiorrhiza Bunge (dan-shen in Chinese) is an important herb in Chinese traditional medicine and has been widely used in Asia to treat various diseases, such as inflammation, diabetes, atherogenesis [1], allergic asthma, and cardiovascular disease [2]. Tanshinones, which are abietane diterpene pigments with a 1,2- or 1,4-naphthoquinone skeleton, are major lipophilic bioactive constituents of dan-shen[3,8]. (+)-isocryptotanshinone (**1**), (+)-neocryptotanshinone (**2**), (-)-cryptotanshinone (**3**), tanshinone IIA (**4**), tanshinone I (**5**), (-)-dihydrotanshinone I (**6**), and miltirone (**7**) [4-6] are well-known examples of tanshinones (**Figure 1**).

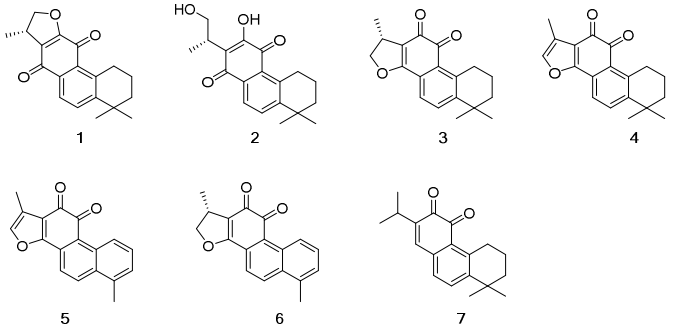
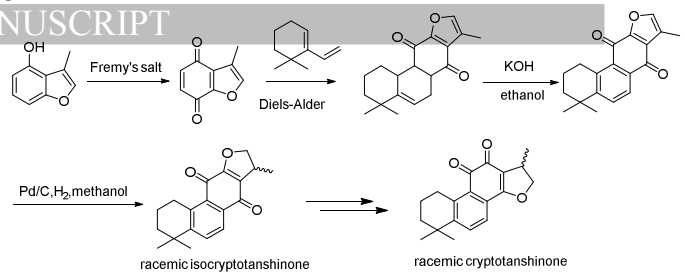


Figure 1. Structures of (+)-isocryptotanshinone (**1**), (+)-neocryptotanshinone (**2**), (-)-cryptotanshinone (**3**), tanshinone IIA (**4**), tanshinone I (**5**), (-)-dihydrotanshinone I (**6**), and miltirone (**7**).

Among these tanshinones, cryptotanshinone, which contains a 1,2-naphthoquinone skeleton, displays several interesting pharmacological properties. For example, it is an effective inhibitor of signal transducer and activator of transcription 3 (STAT3) [7] and exhibits significant cytotoxicity against a number of cultured human tumor cell lines [8]. Due to its remarkable bioactivities, cryptotanshinone has attracted considerable attention from organic chemists. Several total syntheses of cryptotanshinone have already been reported, but most chemical syntheses provide only the racemic form [9,10,11,16] and the only asymmetric syntheses of **3**, which used photochemical aromatic annulation, was reported by Danheiser et al. in 1995 [6]. In addition to 1,2-naphthoquinone skeleton tanshinones, (+)-isocryptotanshinone (**1**) is a lipophilic component with a 1,4-naphthoquinone skeleton isolated from dan-shen. Because of its 1,4-naphthoquinone skeleton, **1** is a more potent STAT3 inhibitor than **3** [12]. **1** inhibits STAT3 signal proteins by inhibiting the MAPK pathway and JAK-STAT signaling pathway, and thus has a strong inhibitory effect on the growth of A549 and MCF-7 cancer cells [12,13]. Furthermore, **1** can also inhibit gastric cancer cell proliferation by inducing G1/G0 cell cycle arrest and apoptosis via inhibiting the STAT3 signaling pathway [14]. The STAT3 pathway is a new target associated with cancer. However, despite its attractive biological activity, the limited availability of **1** from natural sources [15] has seriously hampered further biological research and development. To our knowledge, no asymmetric total synthesis of **1** has been reported and only Inouye and Kakisawa have reported the synthesis of racemic isocryptotanshinone via a Diels−Alder reaction as an intermediate while studying the total synthesis of racemic **3** in 1969 (**Scheme 1**) [16]. Though Inouye and Kakisawa's synthesis is concise, an inherent drawback associated with their synthesis is the lack of enantioselectivity. Hence, the development of an efficient, scalable asymmetric synthetic strategy is worth exploring.

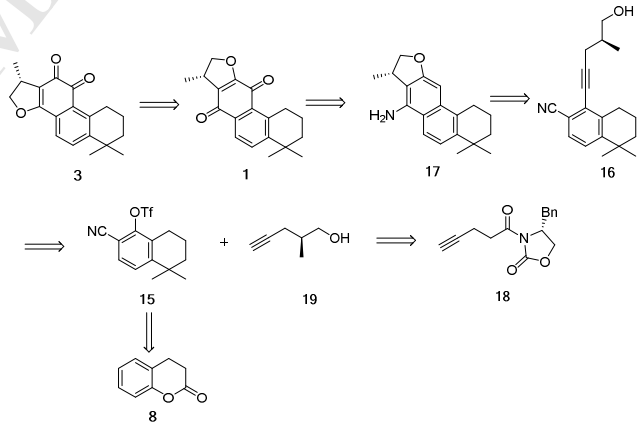


Scheme 1. Inouye and Kakisawa's Diels–Alder reaction strategy for the synthesis of raemic cryptotanshinone.

Based on the promising potential of these tanshinones, we developed an asymmetric synthesis of **1**, which included a formal synthesis of **3**.

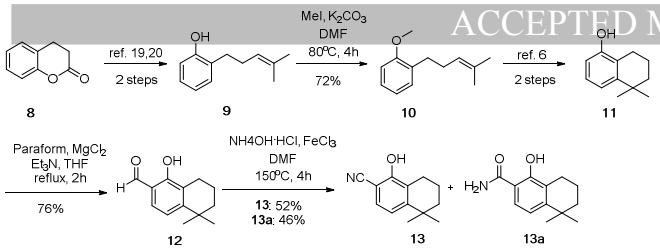
2. Results and discussion

The retrosynthetic analysis for **3** and **1** are shown in **Scheme 2**. Natural product **3** could be obtained from **1** in two steps according to the reported method [6, 27]. And then we anticipated that an oxidation reaction would transform compound **17** into natural product **1**. Compound **17**, the key intermediate, could be constructed via the new base-mediated cyclization strategy reported by Tsai et al. by simply heating compound **16** with NaOMe [17]. In addition, the Sonogashira coupling of intermediate **15** and (S)-2-methylpent-4-yn-1-ol (**20**) would provide compound **16**. Tetralin triflate ester **15** could be obtained through a series of conventional reactions by using commercially available dihydrobenzopyrone (**8**) as the starting material and the chiral side chain (**20**) could be generated from **18** [18,19].



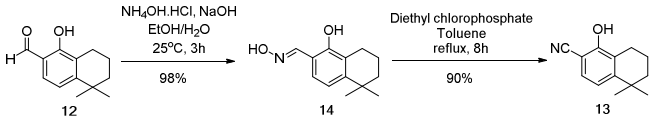
Scheme 2. Retrosynthetic analysis of **1** and **3**.

Our synthesis commenced with known intermediate **9**, which was prepared through a reported protocol [20, 21] from commercially available dihydrocoumarin (**8**) (**Scheme 3**). Treatment of compound **9** with MeI and K_2CO_3 afforded **10** in moderate yield. Using the method reported by Danheiser et al. [6], tetrahydronaphthalen-1-ol (**11**) could be synthesized from **10** in good overall yield. Formylation of **11** with paraformaldehyde and Et_3N in the presence of anhydrous $MgCl_2$ gave **12** [22]. To prepare cyanide **13**, we initially treated salicylaldehyde **12** with hydroxylamine hydrochloride in the presence of $FeCl_3$ to afford cyanide **13** [23]. However, a mixture of desired cyanide **13** and by-product amide **13a** (~1:1) was produced.



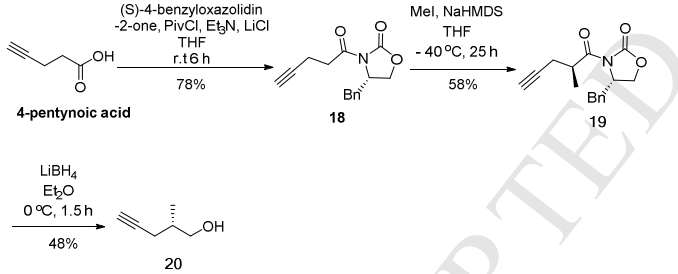
Scheme 3 Synthesis of intermediates **13** and **13a**.

To avoid the formation of **13a**, another synthetic strategy was adopted (**Scheme 4**). According to the synthetic method for nitriles reported by Sardarian et al. [24], oxime **14** was synthesized by the reaction of **12** with hydroxylamine hydrochloride at room temperature in excellent yield. **14** underwent a dehydration reaction with diethyl chlorophosphate to give **13** in great yield (90%).



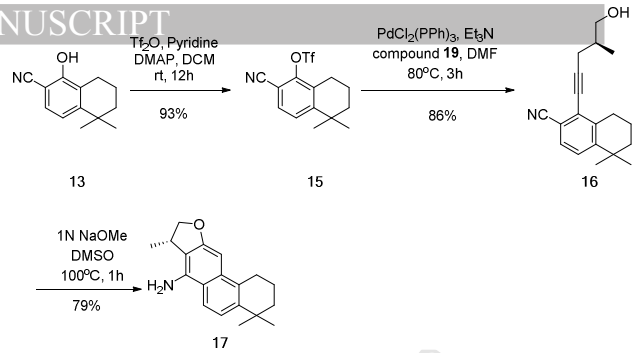
Scheme 4. Synthetic route for intermediate **13**.

The chiral chain (S)-2-methylpent-4-yn-1-ol (**20**) was prepared by Evans alkylation (**Scheme 5**). Thus, acylation of 4-pentynoic acid and oxazolidinone produced compound **18** in a good yield [18]. Then treatment of compound **18** with MeI and NaHMDS at -40°C afforded **19** in a moderate yield. The reduction of compound **19** gave the chiral chain **20** following the reported protocol [19].

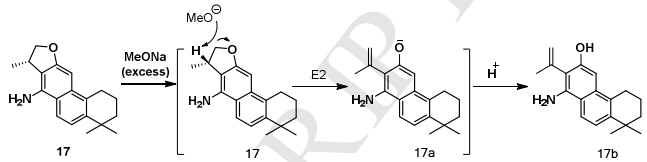


Scheme 5. Synthetic route for intermediate **20**

Then the key intermediate **17** was tried to synthesized (**Scheme 6**). Compound **13** was treated with Tf_2O in the presence of pyridine at room temperature to give intermediate **15** in excellent yield [25]. Subsequently, the Sonogashira coupling of compound **15** and (S)-2-methylpent-4-yn-1-ol (**20**) gave compound **16** in good yield [26]. Treating **16** with 1.5 N NaOMe in DMSO at 140 °C [17] (**Table 1**, Entry 1) afforded only a small amount of desired product **17** along with a large amount of by-product **17b**, a ring-opened product of target compound **17**. The proposed mechanism for the ring-opening of **17** to **17b** is shown in **Scheme 7**. The compound **17b** was probably formed via an E2 elimination reaction from compound **17**. Excess MeONa was likely the main reason to cause the formation of byproduct **17b**. To improve the yield of the cyclization reaction, different reaction conditions were screened (**Table 1**). The best yield (79%) was achieved with 1 N NaOMe at 100 °C (**Table 1**, Entry 4).

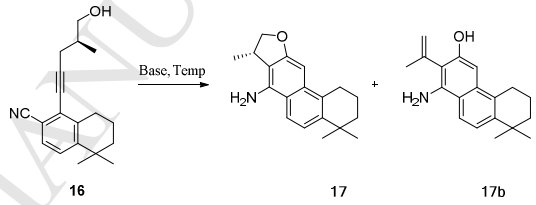


Scheme 6. Synthesis of intermediate **17**.



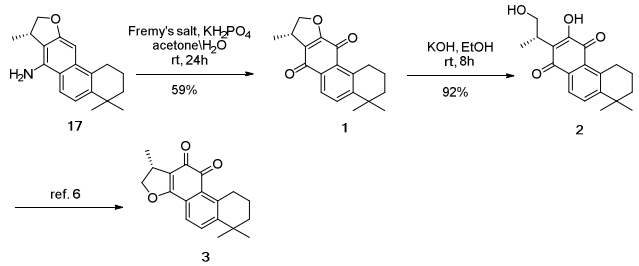
Scheme 7. Proposed mechanism for the formation of **17b**.

Table 1. Optimization of the Base and Temperature for the Cyclization Reaction of **17**



Entry	Catalyst	Temp. ℃	Time (h)	NaOMe (eq.)	Yield (**17b**/**17**)%
1	-	140	0.5	1.5	42/26
2	-	140	0.5	1.0	27/44
3	-	100	1.0	1.5	24/60
4		100	1.0	1.0	-/79
5	18-Crown-5	100	1.0	1.0	-/77

With compound **17** in hand, we continued to synthesize natural product **1** (**Scheme 8**). Oxidation of **17** with Fremy's salt in acetone/H_2O afforded natural product **1** in moderate yield. The present route also includes the formal total synthesis of **3** from **1** in two steps [6, 27].



Scheme 8. Synthesis of **1** and **3**.

3. Conclusion

In conclusion, we performed the first asymmetric total synthesis of the natural product (+)-isocryptotanshinone (**1**). The synthesis was achieved with a Wittig reaction, Friedel–Crafts cyclization, Sonogashira coupling, and alkali-mediated cyclization of an o-cyanophenylalkenyl alcohol as the key steps. The strategy developed here includes the formal synthesis of (-)-cryptotanshinone (**3**) and can be used to provide sufficient amounts of **1** and **3** for further biological activity research.

4. Experimental section

4.1. General description

All reagents were obtained from commercial sources and used without further purification. All NMR experiments were carried out on a Mercury 400 or Bruker AV500 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as the internal standard. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. The following multiplicity abbreviations are used: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad, (dd) double doublet, (dt) double triplet. High-resolution mass spectra (HRMS) were obtained with Thermo Exactive Orbitrap plus spectrometer. Optical rotations were measured with a PerkinElmer Polarimeter 341LC at 589 nm and 20 ºC. IR spectra were recorded on a Thermo Nicolet 5700 FT-IR microscope Centaurs spectrophotometer. Column chromatography was carried out on silica gel (100-200 mesh). Thin-layer chromatography was performed using commercially available HSGF 254 precoated plates.

*4.2. 1-methoxy-2-(4-methylpent-3-en-1-yl)benzene (**10**)*

To a solution of **9** (30.6 g, 173.6 mmol) in DMF (300 mL) was added anhydrous potassium carbonate (35.2 g, 254.6 mmol) and iodomethane (15.6 mL, 250.1 mmol). The mixture was stirred under an Ar atmosphere for 12 h at 80 ºC before being cooled to room temperature. The resulting mixture was poured into water (500 mL) and the aqueous phase was extracted with EtOAc (3×300 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo* to give compound **10** (23.4 g, 72%) as a yellow oil, which was used in the next step without further purification. R_f (**10**) = 0.47 (EtOAc/PE = 1/30). IR (neat): 2959, 2925, 2856, 1601, 1589, 1494, 1463, 1440, 1377, 1243, 1176, 1036, 806, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (dt, J = 1.8 Hz, 7.6 Hz, 1H, Ar-H), 7.13 (dt, J = 1.8 Hz, 7.4 Hz, 1H, Ar-H), 6.87 (dt, J = 1.1 Hz, 7.4 Hz, 1H, Ar-H), 6.83 (d, J = 8.1 Hz, 1H, Ar-H), 5.18-5.23 (m, 1H, C=CH), 3.82 (s, 3H, OCH_3), 2.62 (t, J = 8.1 Hz, 2H, $CH_2\underline{CH_2}Ar$), 2.24 (dd, J = 7.2 Hz, 8.1 Hz, 2H, $\underline{CH_2}CH_2Ar$), 1.69 (d, J = 7.2 Hz, 1.1 Hz, 3H, CH_3), 1.57 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 131.8, 130.9, 129.9, 127.0, 124.4, 120.4, 110.2, 55.2, 30.7, 28.5, 25.8, 17.6; HRMS (ESI): calcd. for $C_{13}H_{19}O$ $[M+H]^+$, 191.1443; found 191.1447.

*4.3. 1-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde (**12**)*

To a solution of **11** (17.6 g, 99.8 mmol) in anhydrous THF (200 mL) was added anhydrous $MgCl_2$ (14.3 g, 150.2 mmol), Et_3N (52.6 mL, 38.1 mmol) and paraformaldehyde (61.6 g, 678.6 mmol) at room temperature. The reaction mixture was stirred at reflux for 24 h under an Ar atmosphere. After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and quenched with 1M aqueous HCl solution. The organic layers were separated and the aqueous layer was extracted with EtOAc (3×300 mL). The combined organics were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (EtOAc/PE = 1/30) to afford compound **12** (15.6 g, 76%) as a yellow oil. R_f (**12**) = 0.54 (EtOAc/PE = 1/20). IR (neat): 3275, 3045, 2948, 2856, 2749, 2673, 1896, 1649, 1573, 1382, 1308, 1229, 875, 746, 712, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.41 (s, 1H, CHO), 9.80 (s, 1H, OH), 7.33 (dt, J = 0.5 Hz, 8.2 Hz, 1H, Ar-H), 7.01 (d, J = 8.2 Hz, 1H, Ar-H), 2.70 (t, J = 6.5 Hz, 2H, CH_2), 1.78-1.83 (m, 2H, CH_2), 1.65-1.68 (m, 2H, CH_2), 1.30 (s, 6H, CH_3×2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 159.8, 156.1, 130.1, 125.4, 118.1, 117.4, 38.5, 34.8, 31.1, 23.1, 18.5. HRMS (ESI): calcd. for $C_{13}H_{17}O_2$ $[M+H]^+$, 205.1223; found 205.1220.

*4.4. (E)-1-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde oxime (**14**)*

To a solution of hydroxylamine hydrochloride (6.1 g, 88.1 mmol) in water (100 mL) was added a solution of sodium hydroxide (3.5 g, 88.1 mmol) in water (100 mL) at 0 ºC. After stirring for 10 min at 0 ºC, a solution of **12** (15.0 g, 73.4 mmol) in ethanol (100 mL) was added. The reaction mixture was allowed to stir for 3 h at room temperature. The resulting solution was poured into water (200 mL). The aqueous phase was extracted with EtOAc (3×300 mL), The organic layers were washed with water, saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo* to give compound **14** (15.8 g, 98%) as a red solid. which was used in the next step without further purification. R_f (**14**) = 0.31 (EtOAc/PE = 1/3). IR (neat): 3396, 3226, 3069, 2941, 2867, 1640, 1615, 1564, 1455, 1402, 1302, 1285, 998, 815, 748, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.48 (br, 1H, OH), 8.38 (br, 1H, OH), 8.20 (s, 1H, CH=N), 7.00 (d, J = 8.4 Hz, 1H, Ar-H), 6.97 (d, J = 8.4 Hz, 1H, Ar-H), 2.76 (t, J = 6.4 Hz, 2H, CH2), 1.82-1.86 (m, 2H, CH_2), 1.65-1.68 (m, 2H, CH_2), 1.31 (s, 6H, CH_3×2); ^{13}C NMR δ (100 MHz, $CDCl_3$) δ 154.5, 153.0, 149.9, 127.7, 124.5, 118.2, 112.8, 38.7, 34.2, 31.6, 23.8, 18.8; HRMS (ESI): calcd. for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1332; found 220.1325.

*4.5. 1-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (**13**)*

To a solution of **14** (14.8 g, 67.5 mmol) in toluene (200 mL) was heated to reflux under Ar atmosphere, a solution of diethyl chlorophosphate (29.4 mL, 202.5 mmol) in toluene (100 mL) was added. The reaction mixture was allowed to stir for 8 h at 120 ºC. After that, the resulting solution was cooled to room temperature and poured into water (200 mL). The aqueous phase was extracted with EtOAc (3×300 mL), The organic layers were washed with water, saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (EtOAc/PE = 1/5) to afford compound **13** (12.3 g, 90%) as white solid. R_f (**13**) = 0.51 (EtOAc/PE = 1/3). IR (neat): 3321, 2963, 2942, 2872, 2228, 1606, 1561, 1483, 1442, 1384, 1336, 1240, 1213, 816, 619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.3 Hz, 1H, Ar-H), 6.97 (d, J = 8.3 Hz, 1H, Ar-H), 6.32 (br, 1H, OH), 2.65 (t, J = 6.4 Hz, 2H, CH_2), 1.80-1.83 (m, 2H, CH_2), 1.62-1.65 (m, 2H, CH_2), 1.26 (s, 6H, CH_3×2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 153.7, 128.6, 124.7, 119.3, 117.1, 95.1, 37.9, 34.3, 31.1, 31.1, 23.6, 18.3; HRMS (ESI): calcd. for $C_{13}H_{16}NO$ $[M+H]^+$, 202.1226; found 202.1219.

*4.6. 1-hydroxy-5,5-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxamide (**13a**)*

Compound **13a** as a red solid. R_f (**13a**) = 0.23 (EtOAc/PE = 1/3). IR (neat): 3447, 3329, 3216, 2954, 2939, 2920, 2863, 1638, 1585, 1489, 1458, 1403, 1360, 1257, 798, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 8.5 Hz, 2H, Ar-H), 6.85 (d, J = 8.5 Hz, 2H, Ar-H), 2.69 (t, J = 6.4 Hz, 2H, CH_2), 1.77-1.84 (m, 2H, CH_2), 1.62-1.65 (m, 2H, CH_2), 1.27 (s, 6H, $CH_3\times2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C=O), 160.0, 153.3, 126.2, 122.9, 116.6, 109.0, 38.4, 34.3, 31.2 ($CH_3\times2$), 23.5, 18.6; HRMS (ESI): calcd. for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1332; found 220.1328.

*4.7. (S)-4-benzyl-3-(pent-4-ynoyl)oxazolidin-2-one (**18**)*

To a solution of 4-pentynoic acid (10.1 g, 102.9 mmol) in THF (400 mL) was added triethylamine (27.5 mL, 198.0 mmol) and PivCl (11.7 mL, 95.0 mmol) at 0 °C. The mixture was stirred at 0 ºC under Ar atmosphere for 1 h, and then LiCl (3.7 g, 87.1 mmol) and (S)-4-benzyloxazolidin-2-one (14.0 g, 79.2 mmol) were added . After that, the reaction mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was poured into water (500 mL) and the aqueous phase was extracted with EtOAc (3×400 mL). The combined organic layers were washed with 1M HCl, sat. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on a silica gel column (EtOAc/PE = 1/3) to afford compound **18** (15.9 g, 78%) as a white solid. R_f (**18**) = 0.35 (EtOAc/PE = 1/3). $[\alpha]_{21}^D$ = +98.2 (c 1.4, CH_2Cl_2) (lit 28. $[\alpha]_{20}^D$ = +98.6 (c 1.8, CH_2Cl_2)), ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.35 (m, 3H, Ar-H), 7.20-7.22 (m, 2H, Ar-H), 4.66-4.72 (m, 1H, CH of Ozazolidone), 4.17-4.25 (m, 2H, CH_2 of Ozazolidone), 3.30 (dd, J = 3.2 Hz, 13.4 Hz, 1H, CH of CH_2Ph), 3.12-3.27 (m, 2H, CH≡CCH_2CH_2), 2.79 (dd, J = 9.6 Hz, 13.4 Hz, 1H, CH of CH_2Ph), 2.59 (dt, 2H, J = 7.1 Hz, 2.6 Hz, CH≡CCH_2CH_2), 2.00 (t, J = 2.6 Hz, 1H, C≡CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 153.3, 135.0, 129.3, 128.9, 127.3, 82.5, 68.9, 66.3, 55.0, 37.7, 34.7, 13.5; HRMS (ESI): calcd. for $C_{15}H_{16}NO_3$ $[M+H]^+$, 258.1113; found 258.1125.

*4.8. (S)-4-benzyl-3-((S)-2-methylpent-4-ynoyl)oxazolidin-2-one (**19**)*

To a solution of compound **18** (15.2 g, 59.1 mmol) in THF (400 mL) was add NaHMDS (ca. 2.0 M THF solution, 44.3 mL, 88.6 mmol) at -78 °C. After 30 min, MeI (7.3 mL, 118.2 mmol) was added. The mixture was allowed to warm to -40 °C and stirred under Ar atmosphere for 25 h. After completion of the reaction, the mixture was quenched with AcOH (10 mL) and poured into water (500 mL), the aqueous phase was extracted with EtOAc (3×400 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (EtOAc/PE = 1/5) to afford **19** (9.3 g, 58%, d. r. > 95:1 determined by ^1H-NMR) as a yellow oil. R_f (**19**) = 0.37 (EtOAc/PE = 1/5). $[\alpha]_{21}^D$ = +107.5 (c 1.0, $CHCl_3$);^1H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.35 (m, 3H, Ar-H), 7.20-7.21 (m, 2H, Ar-H), 4.68-4.74 (m, 1H, CH of Ozazolidone), 4.17-4.25 (m, 2H, CH_2 of Ozazolidone), 3.88-3.97 (m, 1H, $CHCH_2$), 3.27 (dd, J = 2.9 Hz, 13.3 Hz, 1H, CH of CH_2Ph), 2.77 (dd, J = 13.3 Hz, 9.5 Hz, 1H, CH of CH_2Ph), 2.38-2.61 (m, 2H, $CHCH_2$), 1.99 (t, J = 2.6 Hz, 1H, C≡CH), 1.33 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2, 153.0, 135.1, 129.4, 128.9, 127.4, 81.6, 69.8, 66.2, 55.3, 37.9, 37.5, 22.2, 17.1; HRMS (ESI): calcd. for $C_{16}H_{18}NO_3$ $[M+H]^+$, 272.1284; found 272.1281.

*4.9. (S)-2-methylpent-4-yn-1-ol (**20**)*

To a solution of compound **19** (9.0 g, 33.2 mmol) in anhydrous Et_2O (100 mL) was added anhydrous EtOH (0.2 mL) and $LiBH_4$ (ca. 2.0 M THF solution, 18.3 mL, 36.5 mmol) at 0 °C. The resulting solution was stirred under Ar atmosphere at 0 °C for 1.5 h. The reaction was quenched with 1M NaOH and poured into water (200 mL).The aqueous phase was extracted with Et_2O (3×100 mL), The organic layers were combined and dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (Et_2O) to afford compound **20** (1.56 g, 48 %) as a colorless oil. $[\alpha]_{25}^D$ = -12.8 (c 1.1, $CHCl_3$)(lit 29. $[\alpha]_{20}^D$ = -11.1 (c 1.05, $CHCl_3$)); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.58 (d, J = 6.2 Hz, 2H, CH_2OH), 2.18-2.32 (m, 2H, $CHCH_2CCH$), 1.98 (t, J = 2.6 Hz, 1H, C≡CH), 1.85-1.94 (m, 1H, $CHCH_2CCH$), 1.62 (br, 1H, OH), 1.01 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 82.5, 69.5, 66.7, 34.8, 22.1, 16.0; GC-MS (EI): 98.03.

*4.10. 2-cyano-5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-1-yl trifluoromethanesulfonate (**15**)*

To a solution of **13** (12.0 g, 59.6 mmol), pyridine (9.6 mL, 119.2 mmol) and DMAP (0.7 g, 5.9 mmol) in CH_2Cl_2 (300 mL) was added Tf_2O (15.1 mL, 89.4 mmol) at 0 ºC. After that, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The resulting solution was poured into ice-water (300 mL). The aqueous phase was extracted with EtOAc (3×300 mL), The organic layers were washed with water, saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (EtOAc/Pe = 1/30) to afford compound **15** (18.4 g, 93%) as a yellow oil. R_f (**15**) = 0.55 (EtOAc/PE = 1/10). IR (neat): 2962, 2870, 2237, 1610, 1553, 1460, 1414, 1216, 1136, 818, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.2 Hz, 1H, Ar-H), 7.47 (d, J = 8.2 Hz, 1H, Ar-H), 2.86 (t, J = 6.3 Hz, 2H, CH_2), 1.80-1.86 (m, 2H, CH_2), 1.69-1.71 (m, 2H, CH_2), 1.32 (s, 6H, $CH_3\times2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 147.3, 132.7, 131.2, 127.4, 120.0, 116.8, 114.3, 104.6, 37.7, 35.0, 31.5, 25.3, 18.3; HRMS (ESI): calcd. for $C_{14}H_{15}F_3NO_3S$ $[M+H]^+$, 334.0719; found 334.0722.

*4.11. (S)-1-(5-hydroxy-4-methylpent-1-yn-1-yl)-5,5-dimethyl-5,6,7,8- tetrahydronaphthalene-2-carbonitrile (**16**)*

To a solution of **15** (2.0 g, 6.0 mmol) in anhydrous DMF (20 mL) was added bis(triphenylphosphine)palladium(II)chloride (0.1 g, 0.14 mmol), compound **20** (1.47 g, 15.0 mmol) and Et_3N (1 mL, 7.0 mmol) in room temperature. The mixture was stirred at 80 ºC for 3 h under Ar atmosphere before being cooled to room temperature. The resulting solution was poured into water (20 mL). The aqueous phase was extracted with EtOAc (3×30 mL). The organic layers were washed with brine and dried over anhydrous Na_2SO_4, The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (EtOAc/PE = 1/2) to afford compound **16** (1.4 g, 86%) as a yellow oil. R_f (**16**) = 0.32 (EtOAc/PE = 1/3). $[\alpha]_{25}^D$ = +5.6 (c 1.0, $CHCl_3$); IR (neat): 3347, 2960, 2932, 2872, 2229, 1725, 1667, 1581, 1460, 1413, 1387, 1040, 829, 756, 692, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.1 Hz, 1H, Ar-H), 7.32 (d, J = 8.1 Hz, 1H, Ar-H), 3.68 (dd, J = 4.1 Hz, 6.7 Hz, 2H, CH_2CHCH_2OH), 2.87 (t, J = 6.5 Hz, 2H, CH_2), 2.60 (d, J = 6.1 Hz, 2H, CH_2CHCH_2OH), 2.01-2.07 (m, 1H, $CH_2CH(CH_3)CH_2OH$), 1.81-1.84 (m, 2H, CH_2), 1.74 (br, 1H, OH), 1.63-1.66 (m, 2H, CH_2), 1.27 (s, 6H, $CH_3\times2$), 1.10 (d, J = 6.7 Hz, CH3) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4,

139.5, 129.3, 127.5, 126.3, 118.8, 112.6, 99.9, 77.8 (CN), 66.7, 38.2, 35.2, 34.6, 31.4, 29.5, 23.5, 19.0, 16.4; HRMS (ESI): calcd. for $C_{19}H_{24}NO$ $[M+H]^+$, 282.1852; found 282.1850.

*4.12. (S)-4,4,8-trimethyl-1,2,3,4,8,9-hexahydrophenanthro[3,2-b]furan-7- amine (**17**)*

To a solution of **16** (1.4 g, 4.9 mmol) in anhydrous DMSO (10 mL) was added NaOMe (0.26 g, 4.9 mmol). The mixture was stirred at 100 ºC under Ar atmosphere for 1 h. After completion of the reaction (monitored by TLC), the mixture was poured into water (20 mL) and the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (EtOAc/PE = 1/3) to afford compound **17** (1.1 g, 79%) as a pink solid. R_f (**17**) = 0.38 (EtOAc/PE = 1/2). $[\alpha]_{24}^{D}$ = +54.9 (c 1.2, $CHCl_3$); IR (neat): 3481, 3389, 3239, 3054, 2948, 2865, 2828, 1883, 1731, 1632, 1592, 1452, 1430, 1384, 804, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.9 Hz, 1H, Ar-H), 7.32 (d, J = 8.9 Hz, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 4.67 (t, J = 8.5 Hz, 1H, CH), 4.27 (dd, J = 3.5 Hz, 8.5 Hz, 1H, CH), 4.11 (br, 2H, NH_2), 3.50-3.58 (m, 1H, CH), 3.00 (t, J = 6.4 Hz, 2H, CH_2), 1.93-1.99 (m, 2H, CH_2), 1.73-1.76 (m, 2H, CH_2), 1.38 (d, J = 6.4 Hz, 6H, CH_3×3), 1.37 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 142.7, 138.2, 134.5, 130.1, 121.1, 118.0, 117.6, 114.1, 91.9, 78.7, 38.7, 34.4, 34.0, 31.4, 31.3, 27.3, 19.5, 18.3; HRMS (ESI): calcd. for $C_{19}H_{24}NO$ $[M+H]^+$, 282.1852; found 282.1848.

*4.13. 1-amino-8,8-dimethyl-2-(prop-1-en-2-yl)-5,6,7,8-tetrahydrophenanthren-3-ol (**17b**)*

Compound **17b** as a red solid. R_f (**17b**) = 0.42 (EtOAc/PE = 1/2). IR (neat): 3477, 3388, 3317, 3200, 2961, 2926, 2865, 1680, 1650, 1589, 1561, 1422, 827, 783 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H, OH), 7.73 (d, J = 8.9 Hz, 1H, Ar-H), 7.14 (d, J = 8.9 Hz, 1H, Ar-H), 6.55 (s, 1H, Ar-H), 5.36 (s, 1H, C=CH_2), 5.09 (s, 2H, NH2), 4.87 (s, 1H, C=CH_2), 2.78 (t, J = 6.2 Hz, 2H, CH_2), 1.98 (s, 3H, CH_3), 1.84-1.87 (m, 2H, CH_2), 1.63-1.65 (m, 2H, CH_2), 1.28 (s, 6H, CH_3×2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.8, 141.9, 141.5, 141.1, 132.9, 127.7, 120.7, 119.8, 116.5, 115.8, 112.9, 94.7, 38.6, 33.8, 31.3, 26.7, 23.2, 19.3; HRMS (ESI): calcd. for $C_{19}H_{24}NO$ $[M+H]^+$, 282.1852; found 282.1851.

*4.14. (+)-isocrytotanshinone (**1**)*

To a solution of KH_2PO_4 (1.6 g, 11.4 mmol) in H_2O (50 mL) and acetone (100 mL) was added **17** (1.1 g, 3.8 mmol), The mixture was stirred at room temperature for 10 min, and then introduced Fremy's salt (3.0 g, 11.4 mmol) before allowing to stiring at room temperature for an additional 24 h. After completion of the reaction (monitored by TLC), the mixture was was poured into water (100 mL) and the aqueous phase was extracted with EtOAc (3×40 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (EtOAc/PE = 1/5) to afford (+)-isocrytotanshinone (**1**) (0.66 g, 59%, 97.7% ee, determined by HPLC) as a light yellow solid. R_f (**1**) = 0.65 (EtOAc/PE = 1/3). $[\alpha]_{20}^{D}$ = +56.4 (c 1.0, dioxane) (lit 30. $[\alpha]^{D}$ = +55.6 (dioxane)); IR (neat): 2961, 2933, 2869, 1669, 1562, 1469, 1405, 1373, 1249, 1186, 1165, 1033, 809, 751, 732 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 1H, Ar-H), 7.70 (d, J = 8.2 Hz, 1H, Ar-H), 4.81 (t, J = 9.4 Hz, 1H, CH), 4.29 (dd, J = 6.5 Hz, 9.4 Hz, 1H, CH), 3.63-3.69 (m, 1H, CH), 3.24 (t, J = 6.5 Hz, 2H, CH_2), 1.79-1.82 (m, 2H, CH_2), 1.64-1.67 (m, 2H, CH_2), 1.38 (d, J = 6.9 Hz, 3H, CH_3), 1.31 (d, J = 1.7 Hz, 6H, $CH_3\times2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3 (C=O), 180.6 (C=O), 160.9, 153.1, 141.0, 132.9, 132.6, 128.8, 125.5, 124.2, 80.3, 37.8, 35.6, 34.9, 32.0, 31.9, 30.0, 19.3, 18.9; HRMS (ESI): calcd. for $C_{19}H_{21}O_3$ $[M+H]^+$, 297.1485; found 297.1479.

*4.15. (+)-neocryptotanshinone (**2**)*

To a solution of (+)-isocrytotanshinone (**1**) (0.5 g, 1.7 mmol) in EtOH (10 mL) was added KOH (1.6 g, 28.9 mmol), The mixture was stirred at room temperature for 8 h. After completion of the reaction (monitored by TLC), the mixture was poured into 1N HCl (100 mL) at 0 ºC and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. The dried solution was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column (EtOAc/PE = 1/3) to afford **2** (0.49 g, 92%, 98.8% ee, determined by HPLC) as an orange-red solid. R_f (**2**) = 0.45 (EtO Ac/PE = 1/2). $[\alpha]_{20}^{D}$ = +6.1 (c 1.0, $CHCl_3$); IR (neat): 3335, 2962, 2932, 2873, 1642, 1564, 1458, 1413, 1380, 1328, 1202, 1028, 803, 759, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (br, 1H, OH), 7.98 (d, J = 8.1 Hz, 1H, Ar-H), 7.73 (d, J = 8.1 Hz, 1H, Ar-H), 3.81-3.95 (m, 2H, $(CH_3)CH\underline{CH_2}OH$), 3.41-3.48 (m, 1H, $(CH_3)\underline{CH}CH_2OH$), 3.23 (t, J = 6.4 Hz, 2H, CH_2), 2.41 (br, 1H, OH), 1.80-1.85 (m, 2H, CH_2), 1.64-1.68 (m, 2H, CH_2), 1.31 (s, 6H, CH_3×2), 1.26 (d, J = 7.0 Hz, 3H, $(\underline{CH_3})CHCH_2OH$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4 (C=O), 182.9 (C=O), 154.1, 152.9, 140.9, 133.5, 132.6, 126.4, 125.1, 122.9, 65.5, 37.7, 34.8, 33.0, 31.8, 29.9, 19.1, 14.6; HRMS (ESI): calcd. for $C_{19}H_{23}O_4$ $[M+H]^+$, 315.1591; found 315.1598.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://

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