Enantioselective synthesis of cis-hydrobenzofurans bearing all-carbon quaternary stereocenters and application to total synthesis of (−)-morphine

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(−)-Morphine, which is selected as an essential medicine by World Health Organization, is widely applied in the treatment of the pain-related diseases. Due to its synthetically challenging molecular architecture and important clinical role, extensive synthetic studies of morphine-type alkaloids have been conducted. However, catalytic asymmetric total synthesis of (−)-morphine remains a long-standing challenge. Here, we disclose an efficient enantioselective total synthesis of (−)-morphine in a longest linear sequence of 16 steps. The key transformation features a highly enantioselective Robinson annulation enabled by our spiro-pyrrolidine catalyst to rapidly construct the densely functionalized cis-hydrodibenzofuran framework containing vicinal stereocenters with an all-carbon quaternary center. This asymmetric approach provides an alternative strategy for the synthesis of (−)-morphine and its analogues.
Morphine (1a), initially isolated by Sertürner from opium poppy in 1806, exhibits distinct pharmacological features, such as analgesic and sedative activities. Therefore, it is widely applied in clinical treatment and research. Especially, as the most important drug used for the treatment of human pain, it was listed as an essential medicine by World Health Organization (WHO). Also its analogues were selected as the ideal medicines to cure pain-related diseases. Consequently, (-)-morphine and several related drugs have been continuously ranked among the top 200 pharmaceutical products by prescriptions according to the several statistical information by the Njardarson group. Structurally, morphine has a strained pentacyclic skeleton bearing a densely functionalized cis-hydrodibenzo[2,3]furan core and five continuous chiral centers which include a critical all-carbon quaternary stereocenter (Fig. 1). Its synthetically challenging molecular architecture and indispensable role in clinical application attract broad interests from synthetic chemists, biosynthetic chemists, and pharmaceutical chemists.

Over the past 60 years, extensive synthetic studies of morphine-type alkaloids and derivatives (Fig. 1) have been conducted, resulting in both the discovery of numerous structurally related drugs to solve its undesired side effects and the creative development of more than 30 total as well as formal syntheses based on the design of various strategies to address its potential problems of source supplies from nature. However, catalytic asymmetric total synthesis of (-)-morphine has seldom been reported, and moreover, the lack of efficient asymmetric synthetic approach is still an unsolved issue. Therefore, the exploration of an efficient asymmetric approach toward (-)-morphine is highly needed but challenging.

In the past two decades, our research interest has focused on the efficient syntheses of important bioactive natural products based on the construction of quaternary carbon centers by 1,2-carbon atom migration reactions. In the continuation of this research interest, and further application of our spiro-pyrrolidine (SPD) organocatalysts herein, we report an asymmetric synthetic approach toward (-)-morphine.

Results

Design of synthetic plan. Synthetically, the efficient introduction of a sterically congested quaternary carbon center, especially in a catalytic fashion, is one of the main challenges in the asymmetric synthesis of (-)-morphine. Up to now, there are a few methods having been explored to achieve this purpose, for example, Pd-catalyzed Heck reaction by Overman, Trost and Hudlicky, C-H insertion by White, radical cyclization by Parker, oxidative coupling by Gaunt, Cope rearrangement by Metz, and Opatz, and Claisen rearrangement by Metz. However, all of these approaches to the formation of the quaternary carbon require the use of chiral precursors, and catalytic enantioselective construction of the key all-carbon quaternary stereocenter from achiral substrates has not been developed. More importantly, to our best knowledge, a catalytic asymmetric approach for the assembly of AEC ring system by a direct C-C bond-forming strategy has never been reported. We envisaged our synthetic strategy could solve the above mentioned two challenges in one chemical manipulation, and the corresponding strategy was outlined in Fig. 2. The target molecule 1a would be achieved by the cyclization of known precursor, which could be obtained by the introduction of stereocenter and some functional transformations of the tetracyclic enone. We envisioned the enone could be synthesized by the construction of B ring from tricyclic compound. Based on our recent research results on SPD-catalyzed asymmetric construction of all-carbon quaternary stereocenter, we envisaged an organocatalytic asymmetric Robinson annulation of intermediate IV under suitable reaction conditions could provide this key tricyclic compound. We recognized that the substrate IV could be generated by coupling of ethynyl amide V and bromide, which could be prepared from commercially available compounds and respectively.

The preparation of enone precursor. Our synthesis commenced with the preparation of compound 7 on a gram scale (Fig. 3). Starting from commercially available 3-butyn-1-ol, the protection of the primary alcohol with benzyl group and subsequent treatment with N-methoxy-N-methylcarbamoyl chloride afforded the Weinreb amide 5. The boronation of 5 with B2(PIN)3, followed by Suzuki coupling with ary1 bromide 2 (prepared from 2-bromo-6-methoxyphenol) furnished tri-substituted aromatic compound. Final addition with methylmagnesium bromide followed by deprotection of the acetal group provided the desired precursor.

Optimization of reaction conditions. With a sufficient amount of precursor in hand, we then focused our attention on the exploration of the designed intramolecular Robinson annulation. Initially, different secondary amine catalysts were screened to catalyze the desired reaction of 7 by using benzoic acid as an additive in dichloromethane at room temperature. Although no desired tricyclic product 10 was obtained, the intramolecular Michael adduct 8 was obtained. Due to the lack of precedent for asymmetric synthesis of such cis-hydrodibenzo[2,3]furan skeleton bearing a sterically hindered benzyl quaternary carbon center, the current transformation would be potentially used in the syntheses of bioactive natural products and clinical drug molecules, such as abietane diterpene and drug-galanthamine, which contain a common functionalized cis-hydrodibenzo[2,3]furan nucleus. More importantly, the enantio- and diastereoselectivity of the Michael reaction is vital for the access of an enantioenriched tricyclic product (see Supplementary Table 5). Therefore, the investigation of the initial Michael addition was carried out. Notably, in order to accurately measure the enantiomeric excess (ee) value of the Michael adduct, the resulting aldehyde was transformed into its ethylester derivative by Wittig reaction.

From the results listed in Table 1, the catalysts were found to have a significant influence on the enantioselectivities of the Michael reaction. Proline Cat. 1 failed to promote this process (Table 1, entry 1), while its derivative Cat. 2, Jørgensen-Hayashi catalyst 43–45 Cat. 3, and MacMillan catalyst 46 Cat. 4 could catalyze the desired reaction, albeit with acceptable yields and low to moderate enantioselectivities (Table 1, entries 2–4). To our delight, the SPD catalysts Cat. 5 and Cat. 6 provided the expected product in good enantioselectivities along with the faster reaction rate (Table 1, entries 5–6), and the more hindered SPD catalyst Cat. 6 gave a better result. Therefore, catalyst Cat. 6 was selected for further optimization of other reaction parameters. By decreasing the reaction temperature to −20°C, a higher yield and superior enantioselectivity were obtained (Table 1, entry 8). Next, various solvents and additives were screened at −20°C (see Supplementary Tables 2–3). Fortunately, a significant improved enantioselectivity (89% ee) was observed when 2,6-dimethylbenzoic acid (A2) was used as the additive (Table 1, entry 9).

Encouraged by this result, we thoroughly investigated other benzoic acids with diverse steric and electronic properties (see Supplementary Table 2), and found that 2,4,6-trisopropylbenzoic acid (A3) gave the best enantioselectivity (95% ee), while the more hindered 2,4,6-tirertbutylbenzoic acid (A4) had a negative effect on reaction outcomes (Table 1, entries 10–11). Finally, when the reaction temperature was lowered to −30°C, a slight
improvement of enantioselectivity (96% ee) was observed (Table 1, entry 12). However, further decrease of temperature (–40 °C) was found to be detrimental to this reaction, resulting in a longer reaction time and no additional enhancement of enantioselectivity (Table 1, entry 13).

After establishing the optimal reaction conditions, we also explored the substrate scope of the intramolecular Michael addition (for details, see Supplementary Table 6). The reaction results demonstrated that the SPD catalyst had exhibited unique property (up to 87% yield, 96% ee, >20:1 d.r.) in this Michael addition for the construction of the challenging benzylic quaternary carbon stereocenter. More importantly, the current asymmetric transformation provides a potential platform for the preparation of a series of structurally related natural products or drugs bearing the cis-hydrobenzofuran skeleton.

The enantioselective Robinson annulation. Having successfully developed the SPD-catalyzed intramolecular Michael addition reaction, we turned our attention to the designed intramolecular Robinson annulation. Unfortunately, after screening a number of
The reduction with Ph₃P, led to the aldehyde, which underwent selective ozonolysis of the electron-rich double bond, followed by in 91% yield under the acidic conditions. Subsequently, the yield. The latter was easily transformed to the starting material ratio) in 70% yield, along with an Table 7), which afforded two inseparable isomers iodide was found to give the best results (see Supplementary allylation reagents and reaction conditions, 3,3-dimethylallyl of an allyl group was next investigated. After screening various phine, we turned our attention to assemble B ring (Fig. 5). Therefore, the sequent asymmetric Michael addition/aldol cyclization was next investigated. To our delight, when the enone to allylic alcohol derivative in comparision with the previous processes in the total synthesis of morphine33,49. Removal of benzylic group of 13 in the presence of electron-rich aromatic ring and disubstituted olefins proved to be a troublesome task. Debenzylation under the conventional conditions such as catalytic hydrogenolysis, Birch-type reductive cleavage, or Lewis/Brønsted acids catalyzed cleavage was not investigated (Fig. 4). To our delight, when the crude Michael adduct 8 was treated with p-toluenesulfonic acid in toluene at 90 °C, the desired product 10 was isolated in 66% yield without the loss of enantioselectivity (94% ee). It should be noted that its enantiopurity can be further enhanced after one simple recrystallization (>99% ee, 93% yield) in ethyl acetate. Remarkably, this highly enantioselective Robinson annulation performed well even on a 5 g scale.

**Asymmetric total synthesis of (−)-codeine and (−)-morphine.** After the efficient construction of the AEC ring system of morphine, we turned our attention to assemble B ring (Fig. 5). Attempts to introduce an acetol group or its variants at a-position of enone 10 proved to be difficult. Consequently the introduction of an allyl group was next investigated. After screening various allylation reagents and reaction conditions, 3,3-dimethylallyl iodoide was found to give the best results (see Supplementary Table 7), which afforded two inseparable isomers 11 (about 1:1 ratio) in 70% yield, along with an O-allylation by-product in 29% yield. The latter was easily transformed to the starting material 10 in 91% yield under the acidic conditions. Subsequently, the selective ozonolysis of the electron-rich double bond, followed by reduction with Ph₃P, led to the aldehyde, which underwent Friedel–Crafts type cyclization with a catalytic amount of polyphosphoric acid (PPA) to afford the phenanthrofuran 12 as a single diastereoisomer. Then, the transformation of the rigid and highly strained tetracyclic enone 12 to allylic alcohol 13 was investigated. Selective epoxidation of 12 with hydrogen peroxide gave the α,β-epoxy ketone with high regio- and diastereoselectivity, which was treated with N₂H₄ to afford the allylic alcohol 13 in 54% yield over two steps. The excellent selectivity of the epoxidation on the less-hindered face and the stereospecific rearrangement of the resulting α,β-epoxy ketone produced the allylic alcohol 13 as a single isomer. This two-step procedure provides an alternative and efficient approach to transform enone to allylic alcohol derivative in comparision with the previous processes in the total synthesis of morphine33,49. Removal of benzyl group of 13 in the presence of electron-rich aromatic ring and disubstituted olefins proved to be a troublesome task. Debenzylation under the conventional conditions such as catalytic hydrogenolysis, Birch-type reductive cleavage, or Lewis/Brønsted acids catalyzed cleavage was first investigated, and poor regioselectivity or complex mixtures were observed. After extensive investigations, we found that oxidative debenzylation with excess DDQ in chlorobenzene and water afforded the desired alcohol 14 in 85% yield (based on recovered starting material). The primary alcohol of compound 14 was converted to sulfonamide in preference to the allylic alcohol by a highly regioselective intramolecular Mitsunobu reaction, which was probably due to the less steric hindrance of primary alcohol. Notably, sulfonamide 15 was obtained as an enantiopure compound (>99% ee), thus suggesting no loss of enantioselectivity in the

| Entry | Catalyst | Additive | T [°C] | t [h] | Yield [%] | d.r. | ee [%] |
|-------|----------|----------|--------|------|----------|------|------|
| 1     | 1        | A1       | rt     | 72   | trace    | –    | –    |
| 2     | 2        | A1       | rt     | 72   | 60       | 3:1  | –34  |
| 3     | 3        | A1       | rt     | 24   | 68       | 1:5  | 36   |
| 4     | 4        | A1       | rt     | 72   | 28       | 4:1  | –66  |
| 5     | 5        | A1       | rt     | 2    | 71       | 1:9  | 62   |
| 6     | 6        | A1       | –10    | 10   | 78       | 3:1  | 72   |
| 7     | 6        | A1       | –20    | 24   | 82       | 7:1  | 80   |
| 8     | 6        | A1       | –20    | 20   | 83       | 6:9  | 89   |
| 9     | 6        | A1       | –20    | 20   | 86       | 7:4  | 95   |
| 10    | 6        | A2       | –20    | 40   | 76       | 8:7  | 88   |
| 11    | 6        | A4       | –30    | 48   | 87       | 10:2 | 96   |
| 12    | 6        | A3       | –40    | 96   | 85       | 11:8 | 96   |
| 13    | 6        | A3       | –40    | 96   | 85       | 11:8 | 96   |

Reaction was performed with substrate 7 (0.1 mmol), catalyst (10 mol %), and additive (20 mol %) in 1.0 mL of CH₂Cl₂, and followed by addition of Ph₃P = CHCO₂Et.

a Isolated yield
b Determined by ¹H NMR prior to the addition of Ph₃P.
c Determined by chiral HPLC.
above mentioned chemical transformations. The configuration inversion of allyl alcohol 15 via a sequential one-pot oxidation-reduction process generated the Guillou’s intermediate 16 in high efficiency. For the crucial hydrosilylation reaction of 1 toward the synthesis of (−)-codeine, we developed an efficient method by using lithium 4,4’-di-tert-butylbiphenylyl (LiDBB)51,52 in the presence of t-BuOH, which efficiently afforded (−)-codeine (1b) in 68% yield (50 mg scale). Compared with the classical Birch-type reaction50, photoreduction reaction17 or oxymercuration procedure19,23, this methodology showed a remarkable superiority in terms of reproducibility, synthetic scale, and chemical yield (see Supplementary Table 8). Finally, (−)-codeine was readily converted to (−)-morphine (1a) by demethylation with boron tribromide54 in 81% yield. The spectra data of synthetic (−)-morphine and its X-ray crystal structure (Fig. 1a, 1b) are consistent with the reported ones from literatures7,8.

Discussion

In summary, a concise and catalytic asymmetric total synthesis of (−)-morphine was achieved in a longest linear sequence of 16 steps from commercially available 3-buten-1-ol. The highly efficient enantioselective SPD-catalyzed Michael addition/PTSA-catalyzed cyclization sequence not only constructs the AEC tricyclic skeleton and the vicinal stereocenters of the target molecule, but also exhibits superior catalytic properties of SPD catalyst (up to 87% yield, 96% ee) in the initial Michael addition event. Moreover, the current study based on this key methodology enriches the synthetic strategy toward (−)-morphine concerning direct and catalytic asymmetric construction of the challenging all-carbon quaternary stereocenter. Additionally, except for the Suzuki reaction, other chemical transformations can be accomplished under transition-metal-free conditions, which meets the requirement of green chemistry in drug synthesis. Meanwhile, this synthetic route also provides an alternative approach to prepare diverse derivatives of morphine for their further bioactive evaluations to address its potential clinical and social problems. Further applications of the SPD-catalyzed tandem reaction for the diverse syntheses of other natural products is ongoing in our group.

Methods

General information. All moisture- or oxygen-sensitive reactions were carried out under argon atmosphere in oven-dried flasks. All solvents were purified and dried by standard techniques, and distilled prior to use. Unless otherwise noted, all reagents were analytically pure and used without further purification. All reactions were monitored by thin-layer chromatography (TLC), and the products were purified by flash column chromatography. NMR spectra were recorded in CDCl₃ solution on Bruker AM-400 MHz or Varian Mercury-600 MHz instruments and calibrated by using residual undeuterated solvent CHCl₃ (7.26 ppm) or tetramethylsilane (0.00 ppm) as internal reference for 1H NMR and the deuterated methylsilane (0.00 ppm) as internal reference for 13C NMR. High-resolution mass spectra (HRMS) were measured by means of the ESI technique on Fourier transform ion cyclotron resonance mass analyzer. Chiral high performance liquid chromatography (HPLC) analysis data were recorded on a Waters e-2695 instrument equipment with Waters 2998 U/V/Visible detector. The X-ray single-crystal determination was performed on an Agilent SuperNova single crystal X-ray diffractometer.

General procedure for the one-pot Michael addition/Wittig reaction. To a stirred solution of the substrate 7 (36.8 mg, 0.1 mmol) in dry dichloromethane (1.0 mL) at –30 °C was added sequentially 2,4,6-trisopropylbenzoic acid A3 (5.0 mg, 0.02 mmol) and Cat. 6 (3.8 mg, 0.01 mmol). When the starting material disappeared (monitored by TLC, about 48 h), Ph₃P = CHCO₂Et was added. The reaction was warmed to room temperature and stirred for 30 min. Then the
reaction mixture was directly purified by flash column chromatography on silica gel (petroleum ether: ethyl acetate = 1:1) to give the product 9 (38 mg, 87% yield, 10.2:1 d.r., 96% ee) as a colorless oil.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and the Supplementary Information as well as from the authors upon reasonable request. The X-ray crystallographic coordinates for compound 10 reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under CCDC 1882509. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary Information and chemical compound information are available in the online version of the paper. For the proposed mechanism of the key Michael addition, see Supplementary Figure 2. For NMR analysis and HPLC traces of the compounds in this article, see Supplementary Figures 6-168.

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Author contributions

Q.Z. performed all of the experiments. F.-M.Z. directed the asymmetric Michael reaction and optimized the synthetic route of (+)-morphine. Q.Z., F.-M.Z., and Y.-Q.T. wrote the manuscript. C.-S.Z. prepared substrates for the synthesis of (+)-morphine. S.Z.L. prepared substrates for reaction scope evaluation. J.-M.T. helped the design of Robinson annulation. Y.-Q.T., F.-M.Z., S.-H.W., and X.-M.Z. conceptualized and directed the project. All of the authors discussed the results and commented on the manuscript.

Additional information

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