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Target-oriented multifunctional organocatalysis for enantioselective synthesis of bicyclo[3.3.1]nona-2,6-dien-9-ones. A formal asymmetric synthesis of huperzine A

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ABSTRACT

A target-oriented highly enantioselective multifunctional organocatalytic approach has been developed to construct the bicycle-[3.3.1]nona-2,6-dien-9-one core of (−)-huperzine A for the first time, with up to 95% ee in the gram-scale procedure. The newly established methodology is also eligible to synthesize a variety of bicyclo[3.3.1]nona-2,6-dien-9-ones in high enantiopurities, and thus is useful for the future development of novel huperzine A analogs with medicinal interests.

1. Introduction

Huperzine A (Hup A, **1** in Fig. 1) is a well-known medicinal alkaloid isolated from Chinese folk herb *Huperzia serrata* in 1986, featuring a unique bicyclo[3.3.1]nona-2,6-dien-9-one core fused with a pyridone and an exocylic ethylidene moiety.[1] Natural (−)-huperzine A has been found to exhibit potent, selective and reversible inhibitory activity targeting acetylcholinesterase (AchE) and can be applied in the treatment of Alzheimer's disease (AD).[2] Recent pharmacological studies also indicate that it exhibits novel neuroprotective effects by regulating protein metabolism of β-amyloid precursors.[3] The promising clinical prospects and unique structural features of huperzine A have made it an extremely attractive target of organic synthesis, and so far, quite a number of synthetic approaches and elegant total syntheses have been reported,[4] since the first total synthesis of (±)-huperzine A by Ji's and Kozikowski's groups independently in 1989.[5] Kozokowski et al. subsequently reported the first asymmetric synthesis of (−)-huperzine A using a chiral–auxiliary approach.[6] Lately, an additional route to *rac*-huperzine A was also disclosed by Kozikowski and co-workers featuring palladium-catalyzed bicycle-annulation.[7] Because (+)-huperzine A was found to exhibit much lower AchE inhibition activity by comparison with its natural enantiomer, asymmetric synthesis of (−)-huperzine A became extremely important.[8] Several catalytic asymmetric approaches for the synthesis of huperzine A have been reported by Chen, Terashima, Bai, Ma, Langlois et al.,[9] applying either chiral base-catalyzed Michael–aldol reactions or chiral ligand controlled palladium-catalyzed annulations. Unfortunately, only limited successes have been achieved in these efforts. It is noteworthy that Bai's palladium-catalyzed bicycloannulation achieved up to 90.3% ee using a chiral ferrocenylphosphine ligand.[9i] For the organocatalyzed approaches, the highest

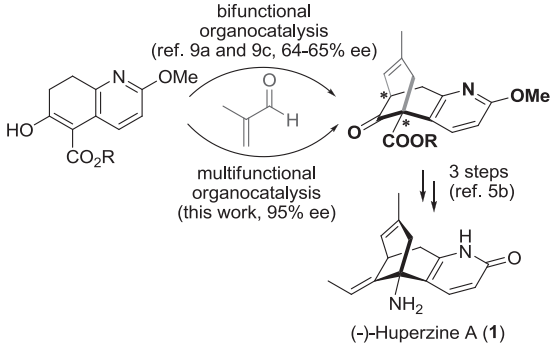

Fig. 1. Tandem Michael–aldol strategy to construct the bicyclo[3.3.1]nona-2,6-dien-9-one core of (−)-huperzine A (**1**).

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selectivity (64–65% ee) was achieved by Chen's and Terashima's groups,[9b,c] respectively, which represents the first application of an organocatalyzed cascade reaction in total synthesis.[10] To date, the endeavor to highly efficient synthesis of *rac*- or (−)-huperzine A is still continuing.[9h,11] Very recently, Fukuyama's and Herzon's groups accomplished two new routes to (−)-huperzine A from enantiopure starting materials, respectively.[11d,e]

Compared to chiral auxiliary-based or chiral-pool approaches, catalytic asymmetric synthesis shall be more economic and efficient. However, catalytic asymmetric synthesis of (−)-huperzine A still keeps challenging especially in generating the unique bicyclo[3.3.1]nona-2,6-dien-9-one core enantioselectively. Though only moderate enantioselectivity has been achieved by Chen[9a] and Terashima et al.,[9c] the tandem Michael–aldol biannulation is still believed as one of the most efficient strategies for the synthesis of bicyclo[3.3.1]nona-2,6-dien-9-one core of (−)-huperzine A (Fig. 1). Considering the rapidly increasing demand of (−)-huperzine A and the on-edge extinction situation of the corresponding natural sources, it is of extreme urgency to develop efficient methodologies and practical asymmetric synthesis of (−)-huperzine A with scalable potential. Evolution of the above mentioned tandem transformation to a highly enantioselective version is one promising direction. Fortunately, recent tremendous advances and new concepts of organocatalysis have established sound foundation for such an endeavor.[12–15] Herein, we wish to report a target-oriented enantioselective Michael addition of sterically hindered α-aryl-β-ketoesters to α-substituted α,β-unsaturated aldehydes using multifunctional organocatalysts, and a scalable procedure for asymmetric synthesis of the bicyclo[3.3.1]nona-2,6-dien-9-one core of (−)-huperzine A (Fig. 1), which represents the first highly enantioselective organocatalytic method for preparing this natural product.

2. Results and discussion

Conjugate additions of β-ketoesters to α,β-unsaturated ketones and α,β-unsaturated aldehydes employing cinchona alkaloid catalysts have been extensively studied by Hermann and Wynberg,[16] Deng and his co-workers,[17] and more recently by Ye's group.[14d] Considering the structural features of substrate in the target transformation (Fig. 1), we proposed that a multifunctional organocatalysis mode might be workable by assistance of proper hydrogen-bonding network. Initially, an amine–thiourea bifunctional organocatalyst **2** (Fig. 2) was applied to catalyze the model reaction between β-ketoester **10a** and methacrolein **11a**.

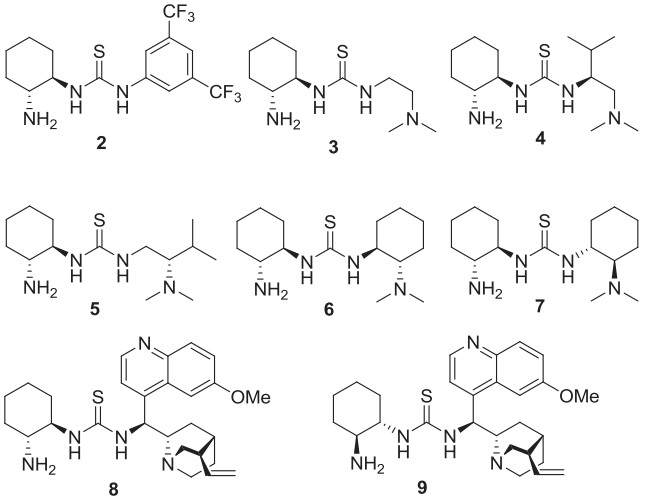
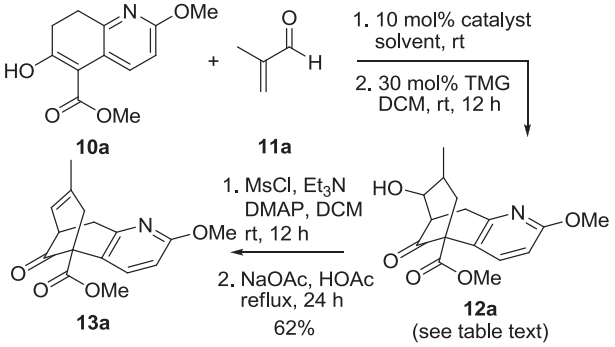


Fig. 2. Organocatalysts applied in this work.

Disappointedly, no desired product could be detected (Table 1, entry 1). Deprotonation of the β-ketoester substrate was speculated to be essential to initiate this reaction, and 1 equiv of NaOAc was decided to add as a weak base (entry 2). After seven days' reaction, alcohol **12a** was obtained in 60% yield. To facilitate the chiral HPLC analysis, this product was further transformed into the corresponding cycloalkene **13a** by known steps.[5b] Though only 70% enantiometric excess was achieved under the conditions with NaOAc, the bifunctional catalytic model was believed to work in this system. We then decided to introduce the third function into the skeleton of catalyst **2** by replacing its 3,5-bis(trifluoromethyl)phenyl group with a tertiary amine moiety (Fig. 2, catalysts **3**–**9**). We assumed that the newly introduced tertiary amine system would act as an intramolecular deprotonation center in the reaction. Higher catalytic efficiency was also expected by improving stereochemical control through the formation of additional hydrogen bonds between the modified catalyst and the substrates. The new multifunctional catalysts **3**–**7** can be easily prepared by condensation of *N*-Boc protected 2-isothiocyanato cyclohexylamine with *N*,*N*-dimethyl-1,2-substituted diamines followed by removal of the *N*-Boc group. To our delight, catalytic Michael

Table 1
Screening of conditions for the Michael–aldol reaction



Entry[a]	Catalyst	Additive	Solvent	*T* [d]	Yield [%][b]	ee [%][c]
1	**2**	—	DCM	7	n.d.	n.d.
2	**2**	NaOAc	DCM	7	60	70
3	**3**	—	DCM	5	86	82
4	**4**	—	DCM	5	83	86
5	**5**	—	DCM	5	90	75
6	**6**	—	DCM	7	84	66
7	**7**	—	DCM	7	87	54
8	**8**	—	DCM	7	92	90
9	**9**	—	DCM	7	91	65
10	**8**	$PhCO_2H$	DCM	1	95	88
11	**8**	$PhCO_2H$	PhMe	2	87	86
12	**8**	$PhCO_2H$	Et_2O	2	83	85
13	**8**	$PhCO_2H$	THF	3	72	82
14	**8**	$PhCO_2H$	EA	4	74	81
15	**8**	$PhCO_2H$	MeOH	7	56	76
16	**8**	$PhCO_2H$	DCM/PhMe[d]	1	90	92 (>99[e])
17[f]	**8**	$PhCO_2H$	DCM/PhMe[d]	3	83	88
18[g]	**8**	$PhCO_2H$	DCM/PhMe[d]	1	87	86
19[h]	**8**	$PhCO_2H$	DCM/PhMe[d]	3	88	92

[a] Unless otherwise noted, the reaction was carried out with **10a** (0.5 mmol), **11a** (5 mmol), catalyst (0.05 mmol) and additive (0.05 mmol) in solvent (2.5 mL) at room temperature.
[b] Isolated yields of **12a** over two steps.
[c] Ee values of **13a** were determined by chiral HPLC, and the absolute configuration of **13a** was assigned by comparing our HPLC results with the reported chiral HPLC retention time (Ref. 9c).
[d] V_{DCM}/V_{PhMe}=1:1.
[e] The ee values were measured by chiral HPLC after one recrystallization of **13a**.
[f] With 5 mol % loading of **8** and $PhCO_2H$.
[g] With 25 mol % loading of **8** and $PhCO_2H$.
[h] Solvent (5 mL) was used.

addition of **10a** to **11a** with the simpler catalyst **3** followed by treatment with TMG provided **12a** in 86% yield, and the ee value of **13a** was improved up to 82% (entry 3). With an (*S*)-configuration isopropyl substitute at the α-carbon of the thiourea moiety, catalyst **4** offered a further improvement (86% ee, entry 4). While, the ee value slightly dropped down to 75% ee if the location of the isopropyl was changed to the β-carbon of ethylenediamine moiety (catalyst **5**, Table 1, entry 5). Application of a more rigid tertiary amine unit by deriving the second *trans*-cyclohexane-1,2-diamine moiety into the catalyst was also attempted (catalysts **6** and **7**). Unfortunately, in both cases, the ee values decreased remarkably (entries 6, 7).

These results suggest that proper combination of primary amine, thiourea, and tertiary amine in the catalyst backbone has a significant impact on enantioselectivity. Inspired by the favorable substituent information from catalyst **4**, we further examined two known catalysts **8** and **9**[14d] with bulkier substituents in the thiourea–tertiary amine system. Both reactions provided high yields of product **12a** (Table 1, entries 8, 9), and the reaction with catalyst **8** afforded **13a** up to 90% ee (entry 8).

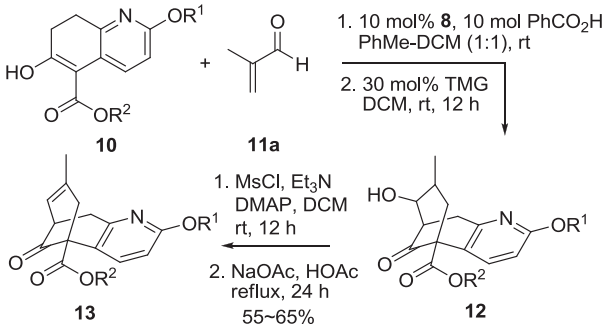
However, relatively longer reaction times (5–7 days) were generally needed to complete these reactions at room temperature. To speed up the catalytic cycle and shorten the reaction time, benzoic acid was added to serve as a co-catalyst. The same Michael reaction could be significantly accelerated and carried out in 24 h with a catalytic amount of benzoic acid. Furthermore, the combined chemical yield of the tandem Michael–aldol reaction was further improved up to 95% (**12a**), and the enantioselectivity of **13a** remained (88% ee, entry 10).

Afterward, five common solvents were screened (Table 1, entries 11–15). It showed that the reaction yields and ee values declined gradually from nonpolar, polar aprotic to protic solvents. Any other single solvents did not give higher enantioselectivity than dichloromethane. Ratio adjustment of the mixed solvents showed that the reaction in a 1:1 mixture of toluene and dichloromethane gave better results (92% ee, entry 16). It is noteworthy here that one recrystallization of the resulting (+)-**13a** (entry 16) from hexane could readily afford the optically pure sample (>99% ee) with 85% recovery yield. In addition, it is found that increasing or decreasing the loadings of the catalyst and brønsted acid could not further improve the enantioselectivity (Table 1, entries 17, 18), and diluting the reaction concentration slowed down the reaction and did not improve the results either (entry 19). Based on the above results, we successfully established the first highly enantioselective organocatalytic approach for the synthesis of the advanced key intermediate of (−)-huperzine A.[5b]

According to the reported total synthesis of *rac*-huperzine A,[5b] the methoxyl protecting group of pyridone moiety in product **13a** would be finally deprotected and the methoxycarbonyl group would be converted into amine via Curtius rearrangement. We therefore surveyed a number of differently substituted β-ketoesters as the Michael donors under the above catalytic conditions. Replacement of the methyl ester with ethyl or benzyl group in the β-ketoester substrate provided the bridged products with slightly decreased ees from 92% to 89% (Table 2, entries 2 and 3). Changing the methoxyl protecting group of the pyridone to bulkier ones, such as ethoxyl or isopropoxyl, did not affect the enantioselectivity of product (entries 4, 5). Alternative of both methyl groups with ethyl groups did not improve the selectivity either (entry 6). Therefore, the size of the protecting groups in substrate **10** demonstrates little influence on the stereoselectivity.

With the optimized conditions, generality of the reaction between α-aryl-β-ketoesters to methacrolein was then explored (Table 3). A variety of substituted β-tetralone substrates **14** smoothly underwent the tandem Michael–aldol reactions, providing the corresponding bridged products **15**. The simplest substrate **14a** gave alcohol **15a** in 78% yield, and the ee vaule of the corresponding alkene **16a** was excellent up to 91% (entry 1). Varying the substituents and their positions on the aromatic ring did not affect the enantioselectivity except **14g** (entries 2–7). The reaction of **14g** only gave a moderate enantioselectivity (65% ee, entry 7), but the enantiopurity could be elevated to an excellent level (98% ee) after only once recrystallization. We believe that all these results should be very useful in future development of novel (−)-huperzine A analogs.

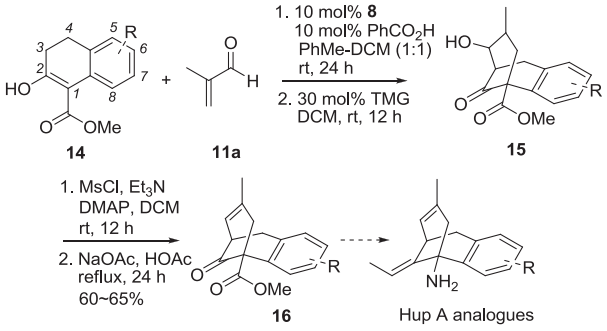
Table 2
Optimization of the protecting groups of **10**



Entry[a]	R^1, R^2	13	Yield [%][b]	ee [%][c]
1	**10a**, R^1=Me, R^2=Me	**13a**	90	92
2	**10b**, R^1=Me, R^2=Et	**13b**	87	92
3	**10c**, R^1=Me, R^2=Bn	**13c**	83	89
4	**10d**, R^1=Et, R^2=Me	**13d**	89	91
5	**10e**, R^1=*i*Pr, R^2=Me	**13e**	93	91
6	**10f**, R^1=Et, R^2=Et	**13f**	88	90

[a] Carried out with **10** (0.5 mmol), **11a** (5 mmol), **8** (0.05 mmol) and $PhCO_2H$ (0.05 mmol) in 2.5 mL of PhMe/DCM (PhMe:DCM=1:1) at room temperature for 24 h.
[b] Isolated yields of **12** over two steps.
[c] ee Values of **13** were determined by chiral HPLC.

Table 3
Examination of the scope of β-kKeto esters

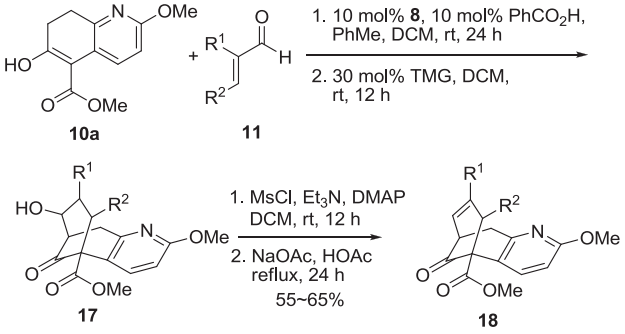


Entry[a]	14 (R)	16	Yield [%][b]	ee [%][c]
1	**14a**, R=H	**16a**	78	91
2	**14b**, R=5-Me	**16b**	83	91
3	**14c**, R=5-OMe	**16c**	82	89
4	**14d**, R=6-OMe	**16d**	88	89
5	**14e**, R=6-Br	**16e**	75	88
6	**14f**, R=7-OMe	**16f**	84	91
7	**14g**, R=7-Me	**16g**	82	65 (98[d])

[a] The reactions were carried out with **14** (0.5 mmol), **11a** (5 mmol), **8** (0.05 mmol) and $PhCO_2H$ (0.05 mmol) in 2.5 mL of PhMe/DCM (PhMe:DCM=1:1) at room temperature for 24 h.
[b] Isolated yields of **15** over two steps.
[c] ee Values of **16** were determined by chiral HPLC method.
[d] The ee value was measured by chiral HPLC after one recrystallization of the product.

Using **10a** as the Michael donor, the scope of Michael acceptors, α,β-unsaturated aldehydes, was also investigated. The reaction with acrolein was completed in a relatively short time (Table 4, entry 2). Disappointingly, its enantioselectivity was very poor (15% ee). With longer branched chains at the α-carbon of the aldehydes, the ee values maintained at a moderate level (75–78% ee, entries 3 and 4). The reactions could not happen when the β-substituted α,β-unsaturated aldehydes **11e** and **11f** were used as the Michael acceptors (entries 5, 6). These results indicate that the developed hydrogen-bond-based multifunctional catalytic mode are very sensitive to the α,β-unsaturated aldehydes 11, and favorable supramolecular interactions existing in the catalytic transition state might be interrupted by large substituent(s) of the α,β-unsaturated aldehydes.

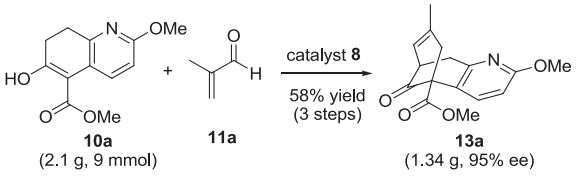
Table 4
Scope of α,β-unsaturated aldehydes



Entry[a]	**11** (R^1, R^2)	Product	Yield [%][b]	ee [%][c]
1	**11a**, R^1=Me, R^2=H	**13a**	90	92
2	**11b**, R^1=H, R^2=H	**18a**	78	15[d]
3	**11c**, R^1=*n*Pr, R^2=H	**18b**	82	78
4	**11d**, R^1=*i*Pr, R^2=H	**18c**	79	75
5	**11e**, R^1=H, R^2=Me	NR[e]	—	—
6	**11f**, R^1=H, R^2=*n*Pr	NR[e]	—	—

[a] The reactions were carried out with **10a** (0.5 mmol), **11** (5 mmol), **8** (0.05 mmol) and $PhCO_2H$ (0.05 mmol) in 2.5 mL of PhMe/DCM (PhMe:DCM=1:1) at room temperature for 24 h.
[b] Isolated yields of **17** over two steps.
[c] ee Values of **18** were determined by chiral HPLC.
[d] Reaction was completed in 2 h.
[e] NR=no reaction.

To examine the scale-up capability of the target transformation, a gram-scale reaction between **10a** (2.1 g) and **11a** was attempted (Scheme 1). To our delight, the bridged product **13a** (1.34 g) was obtained in 58% yield over 3 steps, and more importantly, its enantiopurity was further improved up to 95% ee without any recrystallization. Undoubtedly, the established scalable procedure for highly enantiopure bicyclo[3.3.1]nona-2,6-dien-9-one 13a would be very useful in supplying gram quantities of (−)-huperzine A,[5b] as well as preparation of novel analogs for medicinal researches in the future.



Scheme 1. Scale-up of the organocatalytic Michael reaction.

A possible transition state is proposed to explain the above enantioselective outcome from the Michael reaction (Fig. 3). We

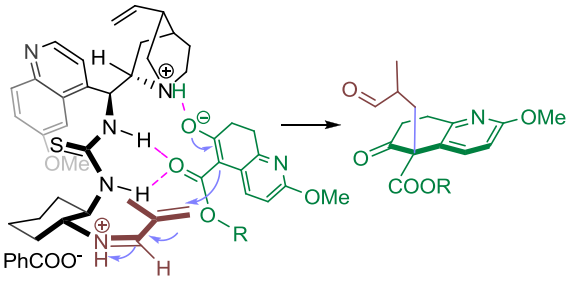


Fig. 3. Proposed transition state of the Michael reaction.

speculate that the β-ketoester is deprotonated by the basic quinuclidine nitrogen, and hydrogen-bonding network is formed between the thiourea moiety and the Michael donor. Simultaneously, iminium activiation of methacrolein by the primary amine of the catalyst and benzoic acid generates an electron-deficient species, which is easily attacked by the electron-rich donor, providing the major stereoisomer. Due to the *trans*-1,2-diamine stereochemistries in catalyst **8** and multiple hydrogen bonds formed between **8** and **10a**, the supramolecular catalytic system provides a suitable cave to accommodate the Michael acceptor methacrolein **11a**. Either the α- or β-substitution of the α,β-unsaturated aldehyde is enlarged, the favorable hydrogen-bond network will be interrupted. According to this model, varying the methyl ester and methyl ether moieties of substrate **10a** or replacement of the pyridine moiety with other aromatic rings has little impact on the supramolecular catalytic transition state because these elements are located outside the cave and far away from the catalytic center.

3. Summary

In conclusion, we have successfully established, as the first example, a highly enantioselective organocatalytic method to construct the bicyclo[3.3.1]nona-2,6-dien-9-one core of (−)-huperzine A and therefore accomplished a formal asymmetric synthesis of this medicinally important natural product. The newly developed target-oriented multifunctional organocatalytic Michael addition of α-aryl-β-ketoesters to α-substituted α,β-unsaturated aldehydes is advantageous to prepare the bicyclo[3.3.1]nona-2,6-dien-9-one core with up to 95% ee in the gram-scale procedure under mild conditions. In addition, it is also eligible to prepare a variety of highly enantiopure bicyclo[3.3.1]nona-2,6-dien-9-one derivatives and thus provides a powerful tool for further development of novel (−)-huperzine A analogs with medicinal interests.

4. Experimental section

4.1. General

All reactions were conducted using oven-dried glassware. Tetrahydrofuran was dried over Na with benzophenone as indicator. Toluene, dichloromethane, petroleum ether, and ethyl acetate were obtained from commercial suppliers and used without further distillation. All melting points were measured with the samples after column chromatographies (without recrystrallization) and uncorrected unless stated. ^{1}H NMR spectra were recorded at 300 or 400 MHz, and ^{13}C NMR spectra were recorded at corresponding instruments in $CDCl_3$ or MeOD using TMS as internal standard. IR spectra were recorded on an FTIR instrument. All new compounds were further characterized by HRMS (high resolution mass spectra). Enantiomeric excess (ee) were determined by HPLC analysis on an Agilent HP 1200 instrument. Optical rotations were measured on a Perkin Elmer 341LC polarimeter.

4.2. Preparation of catalysts 3–7

A mixture of *N*-Boc protected 2-isothiocyanato cyclohexylamine[18] (1.0 equiv) and *N*,*N*-dimethyl-1,2-substituted diamines[19,20] (1.0 equiv) in THF (0.2 M) was stirred for 12 h. The mixture was then concentrated and purified by flash chromatography to afford the thiourea almost quantitatively. The resulting thiourea was dissolved in 4 M HCl–dioxane (3:2, 0.04 M) and stirred overnight to remove the *N*-Boc group. The pH of the resulting mixture was adjusted to 13–14 by adding 1 M aq NaOH. The mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to give the desired catalysts **3**, **4**, **5**, **6**, and **7**.

*4.2.1. 1-((1R,2R)-2-Aminocyclohexyl)-3-(2(dimethylamino)ethyl) thiourea (**3**).* Colorless oil (75% yield over two steps); $[\alpha]_D^{18}$ −6.9 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.67–4.71 (m, 1H), 3.32–3.58 (m, 2H), 2.43–2.45 (m, 3H), 2.19 (s, 6H), 1.87–1.98 (m, 2H), 1.65–1.66 (m, 2H), 1.05–1.29 (m, 4H); ^{13}C NMR (CD_3OD, 75 MHz): δ 183.7, 60.8, 59.3, 56.1, 45.5, 42.8, 34.7, 33.0, 26.0, 25.8; IR (KBr) ν_{max} 3299, 2952, 2926, 1504, 1464, 1411, 1258, 1090, 1037, 974 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{25}N_4S$ [M+H$^+$]: 245.1800; found: 245.1810.

*4.2.2. 1-((1R,2R)-2-Aminocyclohexyl)-3-((S)-1-(dimethylamino)-3-methylbutan-2-yl)thiourea (**4**).* Colorless oil (78% yield over two steps); $[\alpha]_D^{18}$ −4.6 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.66–4.68 (m, 1H), 3.91–3.96 (m, 1H), 2.06–2.49 (m, 3H), 2.07 (s, 6H), 2.05–2.07 (m, 1H), 1.82–1.90 (m, 2H), 1.67–1.68 (m, 2H), 0.96–1.24 (m, 4H), 0.91 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (CD_3OD, 75 MHz): δ 184.3, 62.4, 60.9, 57.4, 56.7, 46.1, 34.7, 33.0, 32.7, 26.1, 26.0, 19.2, 18.4; IR (KBr) ν_{max} 3290, 2950, 2921, 1460, 1258, 1099, 1045, 971 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{31}N_4S$ [M+H$^+$]: 287.2269; found: 287.2275.

*4.2.3. 1-((1R,2R)-2-Aminocyclohexyl)-3-((S)-2-(dimethylamino)-3-methylbutyl)thiourea (**5**).* Colorless oil (80% yield over two steps); $[\alpha]_D^{18}$ −3.2 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.70–4.72 (m, 2H), 3.11–3.26 (m, 1H), 2.34–2.48 (m, 1H), 2.35 (s, 6H), 1.88–2.02 (m, 3H), 1.69–1.71 (m, 2H), 1.06–1.37 (m, 5H), 0.93 (dd, *J*=6.4, 27.2 Hz, 6H); ^{13}C NMR (CD_3OD, 75 MHz): δ 183.2, 73.6, 61.2, 56.1, 43.6, 41.6, 35.1, 33.1, 28.7, 26.1, 26.0, 22.6, 20.0; IR (KBr) ν_{max} 3291, 2955, 2927, 1460, 1260, 1099, 1045, 975 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{31}N_4S$ [M+H$^+$]: 287.2269; found: 287.2270.

*4.2.4. 1-((1R,2R)-2-Aminocyclohexyl)-3-((1S,2S)-2-(dimethyl amino) cyclohexyl) thiourea (**6**).* White foam (73% yield over two steps); $[\alpha]_D^{18}$ −6.7 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.75–3.91 (m, 2H), 2.10–2.41 (m, 3H), 2.14 (s, 6H), 1.92–1.95 (m, 1H), 1.55–1.80 (m, 6H), 1.09–1.24 (m, 8H); ^{13}C NMR (CD_3OD, 75 MHz): δ 182.8, 73.6, 67.6, 60.8, 56.5, 40.7, 34.7, 34.4, 33.0, 26.1, 26.0, 25.9, 25.8, 23.3; IR (KBr) ν_{max} 3313, 2955, 2926, 1504, 1465, 1258, 1091, 974 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{31}N_4S$ [M+H$^+$]: 299.2269; found: 299.2265.

*4.2.5. 1-((1R,2R)-2-Aminocyclohexyl)-3-((1R,2R)-2-(dimethyl amino) cyclohexyl)thiourea (**7**).* White foam (82% yield over two steps); $[\alpha]_D^{18}$ −3.9 (*c* 1.0, EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.80–3.82 (m, 1H), 3.41–3.51 (m, 1H), 2.30–2.44 (m, 3H), 2.18 (s, 6H), 1.90–1.94 (m, 1H), 1.61–1.84 (m, 6H), 1.02–1.30 (m, 8H); ^{13}C NMR (CD_3OD, 75 MHz): δ 182.7, 68.0, 67.3, 60.8, 56.3, 40.7, 35.0, 34.2, 33.1, 26.2, 26.1, 26.0, 25.9, 23.6; IR (KBr) ν_{max} 3314, 2955, 2926, 1505, 1465, 1258, 1091, 976 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{31}N_4S$ [M+H$^+$]: 299.2269; found: 299.2263.

4.3. Preparation of β-ketoesters 10b, 10d, 10e, and 10f

The pyridone[21] (1.0 equiv) was stirred with a mixture of Ag_2CO_3 (2.0 equiv) and iodoalkanes (5.0 equiv) in chloroform (0.2 M) in dark at room temperature overnight. The mixture was filtrated, concentrated and purified by flash chromatography to give differently-protected pyridones, which were further refluxed in 5% HCl-acetone (1:1, 0.1 M) overnight. Acetone was removed and the aqueous layer was basified with solid $NaHCO_3$, and then extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting ketone was directly used in the next step. The resulting ketone (1.0 equiv) in certain carbonate was added dropwise to a mixture of NaH (1.1 equiv) in the carbonate (0.2 M) under nitrogen at room temperature. The mixture was refluxed until disappearance of the starting material on the TLC. The reaction was quenched with saturated aq NH_4Cl. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated. Flash chromatography on silica gel gave the β-ketoesters **10b**, **10d**, **10e**, and **10f**.

*4.3.1. Ethyl 6-hydroxy-2-methoxy-7,8-dihydroquinoline-5-carboxylate (**10b**).* White solid (69% yield over three steps); mp 47 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.26 (1H, s), 7.93 (1H, d, *J*=8.7 Hz), 6.57 (1H, d, *J*=8.7 Hz), 4.38 (2H, q, *J*=7.2 Hz), 3.91 (3H, s), 2.94 (2H, t, *J*=7.5 Hz), 2.63 (2H, t, *J*=7.5 Hz), 1.40 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.6, 171.5, 160.9, 151.0, 136.0, 119.9, 107.1, 98.2, 60.9, 53.2, 29.9, 29.0, 14.1; IR (KBr) ν_{max} 3331, 2925, 1778, 1651, 1593, 1358, 1197, 756 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}NO_4$ [M+H$^+$]: 150.1079; found: 150.1074.

*4.3.2. Methyl 2-ethoxy-6-hydroxy-7,8-dihydroquinoline-5-carboxylate (**10d**).* White solid (54% yield over three steps); mp 73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.15 (1H, s), 7.88 (1H, d, *J*=8.7 Hz), 6.53 (1H, d, *J*=8.7 Hz), 4.30 (2H, q, *J*=7.2 Hz), 3.89 (3H, s), 2.92 (2H, t, *J*=7.9 Hz), 2.61 (2H, t, *J*=7.9 Hz), 1.38 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.6, 171.9, 160.7, 151.0, 136.0, 119.5, 107.1, 98.2, 61.5, 51.6, 29.9, 28.9, 14.6; IR (KBr) ν_{max} 3331, 2925, 1778, 1651, 1593, 1358, 1197, 756 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}NO_4$ [M+H$^+$]: 150.1079; found: 150.1075.

*4.3.3. Methyl 6-hydroxy-2-isopropoxy-7,8-dihydroquinoline-5-carboxylate (**10e**).* White solid (73% yield over three steps); mp 39 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.13 (1H, s), 7.87 (1H, d, *J*=8.7 Hz), 6.50 (1H, d, *J*=8.7 Hz), 5.18–5.26 (1H, m), 3.89 (3H, s), 2.91 (2H, t, *J*=7.7 Hz), 2.61 (2H, t, *J*=7.7 Hz), 1.33 (6H, d, *J*=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.5, 171.9, 160.3, 151.1, 135.9, 119.2, 107.8, 98.2, 67.7, 51.6, 29.9, 29.0, 22.0; IR (KBr) ν_{max} 3331, 2925, 1778, 1651, 1593, 1358, 1197, 756 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}NO_4$ [M+H$^+$]: 164.1236; found: 164.1230.

*4.3.4. Ethyl 2-ethoxy-6-hydroxy-7,8-dihydroquinoline-5-carboxylate (**10f**).* White solid (68% yield over three steps); mp 52 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.26 (1H, s), 7.93 (1H, d, *J*=8.7 Hz), 6.53 (1H, d, *J*=8.7 Hz), 4.37 (2H, q, *J*=7.2 Hz), 4.30 (2H, q, *J*=7.2 Hz), 2.92 (2H, t, *J*=7.8 Hz), 2.62 (2H, t, *J*=7.8 Hz), 1.39 (3H, t, *J*=7.2 Hz), 1.38 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.5, 171.5, 160.7, 151.1, 135.9, 119.7, 107.1, 98.2, 61.5, 60.9, 29.9, 29.0, 14.6, 14.1; IR (KBr) ν_{max} 3331, 2925, 1778, 1651, 1593, 1358, 1197, 756 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}NO_4$ [M+H$^+$]: 164.1236; found: 164.1230.

4.4. Preparation of β-ketoesters 14b, 14c, 14d, 14e, 14f, and 14g

To a mixture of NaH (1.1 equiv) in dimethyl carbonate (0.2 M) was added dropwise β-tetralone[22] (1.0 equiv) in dimethyl carbonate (0.2 M) under nitrogen at room temperature. The mixture was

refluxed until disappearance of the starting material on TLC. The reaction was quenched with saturated aq NH_4Cl. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered, and concentrated. Flash chromatography on silica gel gave β-ketoesters **14b**, **14c**, **14d**, **14e**, **14f**, and **14g**.

*4.4.1. Methyl 2-hydroxy-5-methyl-3,4-dihydronaphthalene-1-carboxylate (**14b**).* White solid (86% yield); mp 62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.25 (1H, s), 7.54 (1H, d, J=7.5 Hz), 7.11 (1H, dd, J=7.5, 7.5 Hz), 6.98 (1H, d, J=7.5 Hz), 3.91 (3H, s), 2.79 (2H, t, J=7.5 Hz), 2.53 (2H, t, J=7.5 Hz), 2.31 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.8, 172.4, 134.1, 131.6, 131.2, 127.1, 125.6, 123.9, 100.0, 51.6, 29.0, 23.2, 19.9; IR (KBr) ν_{max} 3331, 2925, 1778, 1651, 1593, 1358, 1197, 756 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}O_3Na$ [M+Na$^+$]: 241.0841; found: 241.0835.

*4.4.2. Methyl 2-hydroxy-5-methoxy-3,4-dihydronaphthalene-1-carboxylate (**14c**).* White solid (85% yield); mp 59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.36 (1H, s), 7.35 (1H, d, J=8.1 Hz), 7.18 (1H, dd, J=8.1, 8.1 Hz), 6.73 (1H, d, J=8.1 Hz), 3.92 (3H, s), 3.84 (3H, s), 2.87 (2H, t, J=7.5 Hz), 2.51 (2H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.6, 172.3, 155.6, 132.6, 126.4, 121.3, 118.7, 107.6, 99.7, 55.4, 51.6, 28.9, 19.2; IR (KBr) ν_{max} 3331, 2925, 1778, 1651, 1593, 1358, 1197, 756 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}O_4Na$ [M+Na$^+$]: 257.0790; found: 257.0784.

*4.4.3. Methyl 2-hydroxy-6-methoxy-3,4-dihydronaphthalene-1-carboxylate (**14d**).* White solid (83% yield); mp 60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.14 (1H, s), 7.61 (1H, d, J=8.7 Hz), 6.77 (1H, d, J=2.7 Hz), 6.72 (1H, dd, J=2.7, 8.7 Hz), 3.91 (3H, s), 3.80 (3H, s), 2.79 (2H, t, J=7.5 Hz), 2.52 (2H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.7, 172.3, 156.9, 134.8, 126.9, 123.8, 113.2, 111.1, 99.4, 55.0, 51.5, 29.3, 28.0; IR (KBr) ν_{max} 3331, 2925, 1778, 1651, 1593, 1358, 1197, 756 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}O_4Na$ [M+Na$^+$]: 257.0790; found: 257.0782.

*4.4.4. Methyl 6-bromo-2-hydroxy-3,4-dihydronaphthalene-1-carboxylate (**14e**).* White solid (89% yield); mp 49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.34 (1H, s), 7.56 (1H, d, J=8.4 Hz), 7.29 (1H, dd, J=2.1, 8.4 Hz), 7.25 (1H, d, J=2.1 Hz), 3.91 (3H, s), 2.78 (2H, t, J=7.5 Hz), 2.52 (2H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.3, 172.0, 135.2, 130.3, 129.8, 129.2, 127.4, 118.1, 99.3, 51.8, 29.1, 27.3; IR (KBr) ν_{max} 3331, 2925, 1778, 1651, 1593, 1358, 1197, 756 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}BrO_3Na$ [M+Na$^+$]: 304.9789, 306.9769; found: 304.9780, 306.9761.

*4.4.5. Methyl 2-hydroxy-7-methoxy-3,4-dihydronaphthalene-1-carboxylate (**14f**).* White solid (91% yield); mp 51 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.40 (1H, s), 7.32 (1H, d, J=2.7 Hz), 7.04 (1H, d, J=8.4 Hz), 6.63 (1H, dd, J=2.7, 8.4 Hz), 3.92 (3H, s), 3.80 (3H, s), 2.76 (2H, t, J=7.5 Hz), 2.53 (2H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.9, 172.3, 158.1, 132.3, 127.5, 125.4, 112.8, 109.1, 99.7, 55.2, 51.7, 29.9, 26.7; IR (KBr) ν_{max} 2957, 1638, 1587, 1564, 1473, 1434, 1311, 1258, 1205, 1051, 1029, 890, 787 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}O_4Na$ [M+Na$^+$]: 257.0790; found: 257.0792.

*4.4.6. Methyl 2-hydroxy-7-methyl-3,4-dihydronaphthalene-1-carboxylate (**14g**).* White solid (90% yield); mp 49 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.29 (1H, s), 7.50 (1H, d, J=0.6 Hz), 7.02 (1H, d, J=7.5 Hz), 6.89 (1H, dd, J=0.6, 7.5 Hz), 3.93 (3H, s), 2.78 (2H, t, J=7.5 Hz), 2.53 (2H, t, J=7.5 Hz), 2.34 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.4, 172.3, 135.7, 130.1, 129.3, 126.9, 126.5, 125.5, 99.8, 51.6, 29.6, 27.2, 21.4; IR (KBr) ν_{max} 2963, 1622, 1606, 1573, 1471, 1453, 1377, 1339, 1313, 1235, 1212, 1095, 935, 880, 793 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}O_3Na$ [M+Na$^+$]: 241.0841; found: 241.0831.

4.5. The tandem Michael–aldol reaction

Preparation of the racemic samples:[21] To a solution of β-ketoester **10a** (1 mmol), 1,1,3,3-tetramethylguanidine (26 μL, 0.2 mmol) in dichloromethane (2.5 mL) was added α,β-unsaturated aldehyde **11a** (10 mmol). The reaction mixture was stirred at room temperature for 12 h and then the solvent was removed under vacuum. The residue was purified by silica gel chromatography to yield the bridged product **12a**. To a solution of the alcohol **12a** (0.5 mmol) and trimethylamine (690 μL, 5 mmol) in 2.5 mL of dichloromethane was added dropwise mesyl chloride (154 μL, 2 mmol) and a catalytic amount of DMAP at room temperature. The solution was stirred for 12 h at room temperature, and then diluted with dichloromethane, washed with satd aq NH_4Cl, dried and concentrated. The above crude product was dissolved in HOAc (10 mL), and NaOAc (48 mg, 0.6 mmol) was added. The solution was heated to reflux for 24 h. After concentration in vacuum, the residue was treated with satd aq $NaHCO_3$, and extracted with ethyl acetate. The combined organic extracts was washed with brine and dried. After concentration in vacuum, the residue was purified by silica gel chromatography to give *rac*-**13a**.

Asymmetric tandem reaction: To a solution of β-ketoester **10a** (0.5 mmol), catalyst **8** (0.05 mmol) and PhCOOH (0.05 mmol) in toluene/dichloromethane (1:1, 0.2 M) was added α,β-unsaturated aldehyde **11a** (5 mmol). The reaction mixture was stirred at room temperature for the time indicated in tables. The solvent was then removed under vacuum. The residue was dissolved in dichloromethane (2.5 mL), and tetramethylguanidine (20 μL, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 12 h, and the solvent was then removed under vacuum. The residue was submitted to a short silica gel column to remove the catalyst from the bridged product **12a** quickly. To a solution of the alcohol **12a**, trimethylamine (690 μL, 5 mmol) and a catalytic amount of DMAP in 5 mL of dichloromethane was added dropwise mesyl chloride (154 μL, 2 mmol) at room temperature. The solution was stirred for 12 h at room temperature, and then diluted with dichloromethane. The mixture was washed with satd aq NH_4Cl, dried and concentrated. The resulting crude product was dissolved in HOAc (10 mL), and NaOAc (48 mg, 0.6 mmol) was added. The solution was heated to reflux for 24 h. After concentration in vacuum, the residue was diluted with satd aq $NaHCO_3$ and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried. After concentration in vacuum, the residue was purified by silica gel chromatography to give **13a**. The procedure for the gram-scale synthesis was enlarged accordingly.

*4.5.1. (5S,9R)-Methyl 2-methoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methano-cycloocta[b]pyridine-5-carboxylate (**13a**).* White solid (56% yield over two steps); mp 157 °C; $[\alpha]_D^{18}$ 11.1 (*c* 1.0, EtOAc, 92% ee) lit.[9c] $[\alpha]_D^{20}$ 69.9 (*c* 1.37, $CHCl_3$, 99% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (1H, d, J=8.6 Hz), 6.62 (1H, d, J=8.6 Hz), 5.42–5.43 (1H, m), 3.92 (3H, s), 3.76 (3H, s), 3.36–3.42 (2H, m), 3.15–3.19 (2H, m), 2.53 (1H, d, J=17.5 Hz), 1.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 171.4, 163.2, 150.6, 137.6, 133.5, 126.5, 123.7, 109.4, 60.1, 53.3, 52.7, 46.9, 46.0, 40.3, 22.2; IR (KBr) ν_{max} 2947, 1745, 1603, 1576, 831 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}NO_4Na$ [M+Na$^+$]: 310.1055; found: 310.1050; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=254 nm, t_R=12.6 min (minor), 16.9 min (major). 95% ee was detected in the gram scale synthesis.

*4.5.2. (5S,9R)-Ethyl 2-methoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methano-cycloocta[b]pyridine-5-carboxylate (**13b**).* White solid (64% yield over two steps); mp 158 °C; $[\alpha]_D^{18}$ 9.1 (*c* 1.0, EtOAc, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (1H, d, J=8.7 Hz), 6.61 (1H, d,

J=8.7 Hz), 5.40–5.43 (1H, m), 4.24 (2H, q, *J*=7.2 Hz), 3.90 (3H, s), 3.34–3.42 (2H, m), 3.11–3.19 (2H, m), 2.50 (1H, d, *J*=17.4 Hz), 1.60 (3H, s), 1.20 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 170.7, 163.0, 150.6, 137.6, 133.5, 126.5, 123.7, 109.4, 61.5, 59.9, 53.3, 46.8, 45.9, 40.3, 22.2, 13.9; IR (KBr) ν_{max} 2975, 1744, 1598, 1458, 1321, 1257, 1043, 833 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}NO_4Na$ [M+Na$^+$]: 324.1212; found: 324.1210; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=254 nm, t_R=19.0 min (minor), 21.7 min (major).

*4.5.3. (5S,9R)-Benzyl 2-methoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methano-cycloocta[b]pyridine-5-carboxylate (**13c**).* Colorless oil (55% yield over two steps); $[\alpha]_D^{18}$ 7.7 (*c* 1.0, EtOAc, 89% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26–7.33 (5H, m), 7.00 (1H, d, *J*=8.7 Hz), 6.54 (1H, d, *J*=8.7 Hz), 5.41–5.44 (1H, m), 5.23 (2H, dd, *J*=12.6, 30.0 Hz), 3.90 (3H, s), 3.35–3.45 (2H, m), 3.13–3.20 (2H, m), 2.51 (1H, d, *J*=17.7 Hz), 1.61 (3H, d, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.3, 170.7, 163.0, 150.6, 137.7, 135.4, 133.4, 128.3, 128.2, 128.1, 126.2, 123.7, 109.3, 67.2, 60.0, 53.3, 46.8, 45.9, 40.3, 22.2; IR (KBr) ν_{max} 2923, 1743, 1600, 1477, 1423, 1325, 1260, 1024, 825, 741, 697 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{21}NO_4Na$ [M+Na$^+$]: 386.1368; found: 386.1359; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=254 nm, t_R=16.6 min (minor), 21.2 min (major).

*4.5.4. (5S,9R)-Methyl 2-ethoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methano-cycloocta[b]pyridine-5-carboxylate (**13d**).* White solid (60% yield over two steps); mp 159 °C; $[\alpha]_D^{18}$ 8.8 (*c* 1.0, EtOAc, 91% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09 (1H, d, *J*=8.7 Hz), 6.58 (1H, d, *J*=8.7 Hz), 5.38–5.41 (1H, m), 4.27–4.34 (2H, m), 3.73 (3H, s), 3.31–3.41 (2H, m), 3.10–3.16 (2H, m), 2.51 (1H, d, *J*=17.4 Hz), 1.59 (3H, s), 1.35 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 171.4, 162.9, 150.6, 137.6, 133.4, 126.1, 123.7, 109.5, 61.7, 60.0, 52.5, 46.8, 45.9, 40.3, 22.2, 14.5; IR (KBr) ν_{max} 2975, 1744, 1598, 1458, 1321, 1257, 1043, 833 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}NO_4Na$ [M+Na$^+$]: 324.1212; found: 324.1214; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=254 nm, t_R=11.1 min (minor), 15.3 min (major).

*4.5.5. (5S,9R)-Methyl 2-isopropoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methano-cycloocta[b]pyridine-5-carboxylate (**13e**).* White solid (62% yield over two steps); mp 73 °C; $[\alpha]_D^{18}$ 7.8 (*c* 1.0, EtOAc, 91% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.08 (1H, d, *J*=8.4 Hz), 6.53 (1H, d, *J*=8.4 Hz), 5.39–5.41 (1H, m), 5.22–5.30 (1H, m), 3.74 (3H, s), 3.31–3.41 (2H, m), 3.10–3.15 (2H, m), 2.51 (1H, d, *J*=17.7 Hz), 1.60 (3H, s), 1.33 (3H, d, *J*=9.0 Hz), 1.30 (3H, d, *J*=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.5, 171.4, 162.4, 150.5, 137.5, 133.4, 125.7, 123.7, 110.0, 68.0, 60.0, 52.5, 46.8, 45.9, 40.4, 22.2, 22.0, 21.9; IR (KBr) ν_{max} 2976, 1636, 1596, 1559, 1464, 1298, 1228, 1109, 1010, 820 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ [M+Na$^+$]: 338.1368; found: 338.1370; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=254 nm, t_R=10.8 min (minor), 14.9 min (major).

*4.5.6. (5S,9R)-Ethyl 2-ethoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methano-cycloocta[b]pyridine-5-carboxylate (**13f**).* White solid (61% yield over two steps); mp 124 °C; $[\alpha]_D^{18}$ 13.5 (*c* 1.0, EtOAc, 90% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09 (1H, d, *J*=8.7 Hz), 6.57 (1H, d, *J*=8.7 Hz), 5.38–5.41 (1H, m), 4.33 (2H, q, *J*=7.2 Hz), 4.23 (2H, q, *J*=7.2 Hz), 3.32–3.41 (2H, m), 3.10–3.16 (2H, m), 2.50 (1H, d, *J*=17.4 Hz), 1.59 (3H, s), 1.36 (3H, t, *J*=7.2 Hz), 1.20 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 170.8, 162.8, 150.6, 137.6, 133.4, 126.3, 123.7, 109.4, 61.6, 61.5, 59.9, 46.8, 45.9, 40.3, 22.1, 14.4, 13.9; IR (KBr) ν_{max} 2976, 1737, 1600, 1485, 1323, 1257, 1024, 845 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ [M+Na$^+$]: 338.1368; found: 338.1360; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=254 nm, t_R=10.1 min (minor), 11.6 min (major).

*4.5.7. (5S,9R)-Methyl 7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methanobenzo-[8]annulene-5-carboxylate (**16a**).* White solid (62% yield over two steps); mp 157 °C; $[\alpha]_D^{18}$ 19.9 (*c* 1.0, EtOAc, 91% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22–7.26 (2H, m), 7.12–7.15 (1H, m), 6.90–6.93 (1H, m), 5.35–5.36 (1H, m), 3.75 (3H, s), 3.38–3.45 (2H, m), 3.14–3.15 (2H, m), 2.62 (1H, d, *J*=17.5 Hz), 1.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.2, 171.2, 139.3, 133.8, 132.7, 128.6, 127.4, 127.5, 126.8, 123.2, 61.5, 52.3, 47.6, 46.2, 37.8, 22.1; IR (KBr) ν_{max} 2920, 2841, 1738, 1578, 1491, 1435, 1352, 1265, 1238, 1163, 1142, 1084, 1034, 999, 970, 954, 912, 831, 756, 725, 654 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}O_3Na$ [M+Na$^+$]: 279.0997; found: 279.1001; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 1.0 mL/min, λ=254 nm, t_R=6.4 min (minor), 9.2 min (major).

*4.5.8. (5S,9R)-Methyl 1,7-dimethyl-11-oxo-5,6,9,10-tetrahydro-5,9-methanobenzo-[8]annulene-5-carboxylate (**16b**).* White solid (59% yield over two steps); mp 106 °C; $[\alpha]_D^{18}$ 8.8 (*c* 1.0, EtOAc, 91% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16 (1H, d, *J*=7.5 Hz), 7.11 (1H, dd, *J*=7.5, 7.5 Hz), 6.78 (1H, d, *J*=7.5 Hz), 5.34–5.36 (1H, m), 3.73 (3H, s), 3.38–3.44 (1H, m), 3.14–3.17 (3H, m), 2.66 (1H, d, *J*=17.4 Hz), 2.25 (3H, s), 1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.8, 172.0, 139.6, 136.4, 133.9, 131.4, 129.1, 127.1, 124.8, 123.6, 61.6, 52.4, 47.8, 45.9, 35.8, 22.1, 19.8; IR (KBr) ν_{max} 2919, 1741, 1725, 1435, 1264, 1248, 1076, 952, 829, 793, 726 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_3Na$ [M+Na$^+$]: 293.1154; found: 293.1155; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=90:10, 1.0 mL/min, λ=210 nm, t_R=6.1 min (minor), 9.1 min (major).

*4.5.9. (5S,9R)-Methyl 1-methoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methanobenzo[8]annulene-5-carboxylate (**16c**).* White solid (64% yield over two steps); mp 95 °C; $[\alpha]_D^{18}$ 11.1 (*c* 1.0, EtOAc, 89% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21 (1H, dd, *J*=7.5, 7.5 Hz), 6.76 (1H, d, *J*=7.5 Hz), 6.51 (1H, d, *J*=7.5 Hz), 5.33–5.36 (1H, m), 3.82 (3H, s), 3.74 (3H, s), 3.28–3.41 (2H, m), 2.98–3.15 (2H, m), 2.65 (1H, d, *J*=17.4 Hz), 1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.8, 171.8, 157.0, 140.7, 133.6, 128.0, 123.7, 122.1, 118.7, 108.5, 61.3, 55.2, 52.4, 47.4, 45.6, 32.5, 22.1; IR (KBr) ν_{max} 2930, 1734, 1584, 1469, 1436, 1259, 1035, 828, 787, 720 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_4Na$ [M+Na$^+$]: 309.1103; found: 309.1100; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=90:10, 1.0 mL/min, λ=210 nm, t_R=7.1 min (minor), 10.8 min (major).

*4.5.10. (5S,9R)-Methyl 2-methoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methano-benzo[8]annulene-5-carboxylate (**16d**).* White solid (63% yield over two steps); mp 100 °C; $[\alpha]_D^{18}$ 8.8 (*c* 1.0, EtOAc, 89% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.83 (1H, d, *J*=8.7 Hz), 6.78 (1H, dd, *J*=2.4, 8.7 Hz), 6.64 (1H, d, *J*=2.4 Hz), 5.34–5.36 (1H, m), 3.78 (3H, s), 3.75 (3H, s), 3.33–3.42 (2H, m), 3.06–3.12 (2H, m), 2.58 (1H, d, *J*=17.7 Hz), 1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.5, 172.0, 158.7, 134.1, 134.0, 131.4, 128.0, 123.2, 113.5, 113.0, 61.0, 55.1, 52.4, 47.6, 46.0, 38.1, 22.2; IR (KBr) ν_{max} 2917, 1741, 1717, 1505, 1319, 1264, 1229, 1024, 848 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_4Na$ [M+Na$^+$]: 309.1103; found: 309.1099; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 1.0 mL/min, λ=210 nm, t_R=8.6 min (minor), 12.5 min (major).

*4.5.11. (5S,9R)-Methyl 3,7-dimethyl-11-oxo-5,6,9,10-tetrahydro-5,9-methanobenzo-[8]annulene-5-carboxylate (**16e**).* White solid (57% yield over two steps); mp 94 °C; $[\alpha]_D^{18}$ 10.1 (*c* 1.0, EtOAc, 88% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (1H, dd, *J*=1.8, 8.4 Hz), 7.29 (1H, d, *J*=1.8 Hz), 6.79 (1H, d, *J*=8.4 Hz), 5.33–5.34 (1H, m), 3.74 (3H, s), 3.33–3.41 (2H, m), 3.06–3.12 (2H, m), 2.56 (1H, d, *J*=17.4 Hz), 1.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 171.2, 138.4, 135.1, 134.0, 131.6, 130.1, 128.6, 123.1, 121.3, 61.2, 52.6, 47.5, 45.8, 37.6, 22.2; IR (KBr) ν_{max} 2913, 1744, 1482, 1433, 1264, 1237, 1082, 1033, 834 cm^{-1};

HRMS (ESI) calcd for $C_{16}H_{15}BrO_3Na$ [M+Na$^+$]: 357.0102, 359.0082; found: 357.0100, 359.0080; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=90:10, 1.0 mL/min, λ=210 nm, t_R=6.4 min (minor), 8.5 min (major).

*4.5.12. (5S,9R)-Methyl 3-methoxy-7-methyl-11-oxo-5,6,9,10-tetrahydro-5,9-methano-benzo[8]annulene-5-carboxylate (**16f**).* White solid (65% yield over two steps); mp 129 °C; $[\alpha]_D^{18}$ 12.8 (*c* 1.0, EtOAc, 91% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (1H, d, *J*=8.4 Hz), 6.80 (1H, dd, *J*=2.4, 8.4 Hz), 6.40 (1H, d, *J*=2.4 Hz), 5.32–5.35 (1H, m), 3.76 (3H, s), 3.75 (3H, s), 3.29–3.39 (2H, m), 3.03–3.11 (2H, m), 2.63 (1H, d, *J*=17.4 Hz), 1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.4, 171.7, 158.4, 140.4, 133.9, 129.7, 124.9, 123.2, 113.5, 111.9, 61.6, 55.2, 52.4, 47.5, 46.3, 37.0, 22.2; IR (KBr) ν_{max} 2952, 1739, 1721, 1612, 1506, 1434, 1330, 1267, 1246, 1232, 1145, 1040, 814 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_4Na$ [M+Na$^+$]: 309.1103; found: 309.1112; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=90:10, 1.0 mL/min, λ=254 nm, t_R=7.1 min (minor), 14.3 min (major).

*4.5.13. (5S,9R)-Methyl 3,7-dimethyl-11-oxo-5,6,9,10-tetrahydro-5,9-methanobenzo-[8]annulene-5-carboxylate (**16g**).* White solid (58% yield over two steps); mp 112 °C; $[\alpha]_D^{18}$ 7.8 (*c* 1.0, EtOAc, 65% ee); $[\alpha]_D^{18}$ 17.9 (*c* 1.0, EtOAc, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.00–7.07 (2H, m), 6.70 (1H, s), 5.33–5.35 (1H, m), 3.76 (3H, s), 3.32–3.40 (2H, m), 3.06–3.11 (2H, m), 2.62 (1H, d, *J*=17.1 Hz), 2.30 (3H, s), 1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.6, 171.9, 139.2, 136.5, 133.9, 129.7, 128.6, 128.5, 127.2, 123.3, 61.5, 52.4, 47.6, 46.3, 37.5, 22.2, 21.0; IR (KBr) ν_{max} 2919, 1740, 1505, 1456, 1433, 1263, 1240, 1224, 1080, 822 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_3Na$ [M+Na$^+$]: 293.1154; found: 293.1150; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=210 nm, t_R=12.3 min (minor), 15.3 min (major).

*4.5.14. (5S,9R)-Methyl 2-methoxy-11-oxo-5,6,9,10-tetrahydro-5,9-methanocyclo-octa[b]pyridine-5-carboxylate (**18a**).* The racemic product was prepared by reported method.[23] Colorless oil (62% yield over two steps); $[\alpha]_D^{18}$ 4.8 (*c* 1.0, EtOAc, 15% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13 (1H, d, *J*=8.6 Hz), 6.63 (1H, d, *J*=8.6 Hz), 5.42–5.49 (2H, m), 3.94 (3H, s), 3.77 (3H, s), 3.30–3.42 (2H, m), 3.15–3.19 (2H, m), 2.54 (1H, d, *J*=17.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 171.4, 163.2, 150.6, 137.6, 133.5, 129.5, 123.4, 109.4, 60.1, 53.3, 52.7, 46.9, 46.0, 40.3; IR (KBr) ν_{max} 2960, 1746, 1610, 1478, 1423, 1267, 1032 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{15}NO_4Na$ [M+Na$^+$]: 296.0899; found: 296.0909; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 1.0 mL/min, λ=254 nm, t_R=8.8 min (major), 10.2 min (minor).

*4.5.15. (5S,9R)-methyl 2-methoxy-11-oxo-7-propyl-5,6,9,10-tetrahydro-5,9-methano-cycloocta[b]pyridine-5-carboxylate (**18b**).* Yellow oil (55% yield over two steps); $[\alpha]_D^{18}$ 11.0 (*c* 1.0, EtOAc, 78% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09 (1H, d, *J*=8.4 Hz), 6.59 (1H, d, *J*=8.4 Hz), 5.39–5.41 (1H, m), 3.89 (3H, s), 3.74 (3H, s), 3.30–3.41 (2H, m), 3.13–3.18 (2H, m), 2.54 (1H, d, *J*=17.4 Hz), 1.78–1.87 (2H, m), 1.21–1.27 (2H, m), 0.66 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.3, 171.3, 163.1, 150.6, 137.4, 137.1, 126.2, 123.3, 109.4, 60.1, 53.3, 52.5, 45.9, 44.9, 40.3, 37.9, 20.3, 13.0; IR (KBr) ν_{max} 2957, 1746, 1600, 1478, 1423, 1325, 1261, 1031, 825 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ [M+Na$^+$]: 338.1368; found: 338.1375; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=254 nm, t_R=11.2 min (minor), 14.2 min (major).

*4.5.16. (5S,9R)-Methyl 7-isopropyl-2-methoxy-11-oxo-5,6,9,10-tetrahydro-5,9-methano-cycloocta[b]pyridine-5-carboxylate (**18c**).* Yellow oil (56% yield over two steps); $[\alpha]_D^{18}$ 10.2 (*c* 1.0, EtOAc, 75% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09 (1H, d, *J*=8.7 Hz), 6.57 (1H, d, *J*=8.7 Hz), 5.38–5.41 (1H, m), 3.88 (3H, s), 3.73 (3H, s), 3.28–3.40 (2H, m), 3.10–3.16 (2H, m), 2.58 (1H, d, *J*=17.1 Hz), 2.06–2.15 (1H, m), 0.84 (3H, d, *J*=6.9 Hz), 0.79 (3H, d, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.4, 171.5, 163.0, 150.7, 142.8, 137.3, 126.1, 121.1, 109.3, 60.1, 53.3, 52.5, 45.9, 42.8, 40.4, 33.8, 21.0, 20.7; IR (KBr) ν_{max} 2955, 1746, 1601, 1478, 1423, 1325, 1261, 1032, 828 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NO_4Na$ [M+Na$^+$]: 338.1368; found: 338.1370; HPLC conditions: Daicel OD-H column, *n*-Hexane/*i*PrOH=95:5, 0.5 mL/min, λ=254 nm, t_R=10.1 min (minor), 12.8 min (major).

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Supplementary data

Supplementary data that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.05.061.

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