Chiral Guanidine Catalyzed Annulation to the Core Structure of (−)-Huperzine A†

PAN, Qiang-Biao[a](潘强彪) **MA, Da-Wei***,[b](马大为)

[a] *Department of Chemistry, Fudan University, Shanghai 200433, China*

[b] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

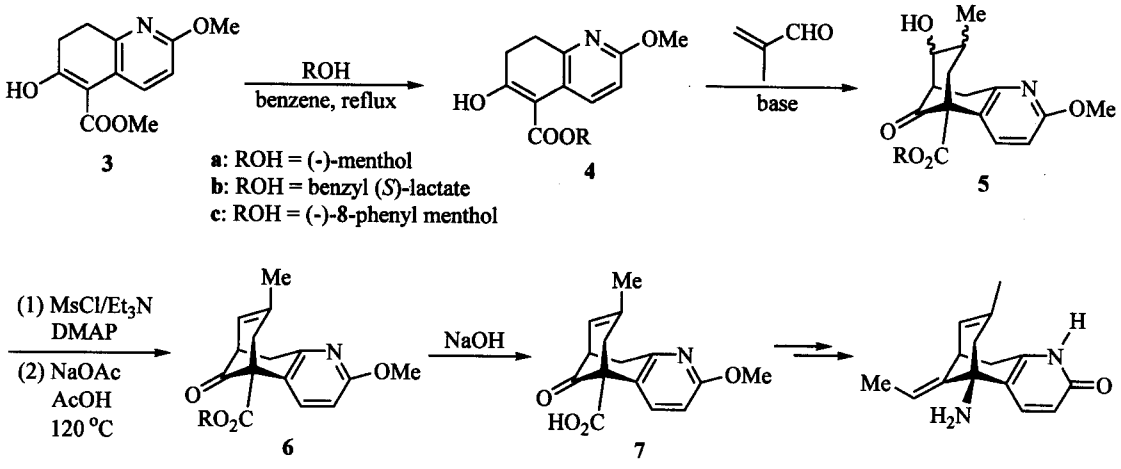
A bridged bicyclic compound (7), the key intermediate for the synthesis of (−)-huperzine A (1), was prepared by diastereoselective Michael-aldol annulation of β-keto ester (4) catalyzed by chiral guanidine (2). A variety of chiral catalysts, substrates and reaction conditions were tested.

Keywords (−)-Huperzine A, chiral catalysts, guanidine, Michael-aldol annulation

(−)-Huperzine A (**1**) is a lycopodium alkaloid isolated from *Huperzia Serrata*, a Chinese folk medicine.[1,2] Biological studies revealed that this compound is a very potent, selective and reversible inhibitor of acetylcholinesterase (AChE).[2-4] In addition, (−)-huperzine A (**1**) was shown to be more selective for AChE than other AChE inhibitors such as tacrine that is in clinical application for treatment of Alzheimer's disease, thereby having potential usage for this disease.[5-7]

Due to some difficulties associated with obtaining a large quantity of **1** from plants,[3] considerable attentions have been directed to the synthetic studies of (−)-huperzine A. Obviously, the major challenge in the synthesis of (−)-huperzine A (**1**) lies in the enantioselective formation of its 1,3,3-bicyclic framework. The first enantioselective synthesis of (−)-huperzine A (**1**) was described by Kozikowski[8] and his co-workers. In their work the key step was a diastereoselective Michael-aldol annulation of a (−)-8-phenyl menthol derived ketoester **4c** (Scheme 1) with methacrolein to affore **5c** diastereoselectively. Unfortunately, this protocol seems to lack practicality because an excessive amount of expensive (−)-8-phenyl menthol is necessary as a chiral auxiliary and the diastereoselectivity (80% *de*) was not excellent. As a result, recently two manners for asymmetrically synthesizing (−)-huperzine A have been intensively studied. One is using the chiral bases to catalyze the Michael-aldol annulation,[9] another one is using Pd-catalyzed enantioselective or diastereoselective allylation/annulation.[9-12] However, no protocol was satisfactory for preparing (−)-huperzine A yet.

Scheme 1



* E-mail: madw@mail.sioc.ac.cn

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Better diastereoselectivity pattern was observed when the substrate was switched to the ester **4b**. In this case the best result (73.2% *de*) was obtained when *trans*-1,2-diaminocyclohexane derived guanidine **2e** was employed as a catalyst (Entry 17). Other catalysts also gave much improved selectivity in comparison with the cases that **4a** was used except for **2c**. These results imply that the diastereoselectivity outcome of this reaction is highly dependent on the chiral auxiliary used. In addition, although (*R*,*R*)-guanidine **2a** and its enantiomer **2b** gave almost same induced result for the reaction of **4b** with methacrolein (compare Entries 13 and 14), the marked diastereoselective difference resulted by **2c** and **2d** clearly indicated that guanidine also gave the contribution for asymmetric induction (compare Entries 15 and 16).

In conclusion, we have demonstrated that some enantiopure guanidines were effective catalysts for diastereoselective Michael-aldol annulation of 5,6,7,8-tetrahydro-2-alkoxy-6-oxo-5-quinolinecarboxylic ester with methacrolein. Although in many cases these catalysts only gave moderate or poor diastereoselectivity, the good results observed in some cases indicated that the present catalysts would provide an efficient and alternate catalyst system for the key step in the synthesis of (−)-huperzine A. Further improvement utilizing other guanidine catalysts and chiral auxiliaries is in progress.

Experimental

The diastereoselectivity of the products was determined by ^{1}H NMR. ^{1}H NMR spectra were recorded with $CDCl_3$ as solvent and tetramethylsilane as internal standard at a Bruker AM-300 spectrometer. All chemical shifts (δ) were reported in parts per million and J values in Hz. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter. Infrared (IR) spectra were measured with a Perkin-Elmer241 Fourier transform spectrometer. Low resolution mass (EIMS) spectra were taken with a HP-5989A spectrometer, and high resolution mass (HREIMS) spectra were obtained on a Finnigan MAT spectrometer.

2-Methoxy-6-oxo-5,6,7,8-tetrahydro-quinoline-5-carboxylic acid (1*R*,2*S*,5*R*)-2-*isopropyl*-5-*methyl-cyclohexyl ester* (**4a**)

A mixture of **3** (556 mg, 2.36 mmol), (−)-menthol (3.68 g, 23.6 mmol) and benzene (15 mL) was refluxed for 48 h. After the mixture was cooled to room temperature, the solvent was removed by rotary evaporation. The residue was purified by flash column chromatography (using 1/10 ethyl acetate/petroleum ether as an eluent) to afford 809 mg (95%) of **4a**.

4a $[\alpha]_D^{20}$ − 82.8 (*c* 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 13.46 (s, 1H), 7.94 (d, J = 8.7 Hz, 1H), 6.56 (d, J = 8.7 Hz, 1H), 5.00 (m, 1H), 3.91 (s, 3H), 2.95 (m, 2H), 2.63 (m, 2H), 2.15 (m, 1H), 1.88 (m, 1H), 1.75—0.98 (m, 7H), 0.94 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.78 (d, J = 7.0 Hz, 3H); IR ν_{max}: 3428.1, 2956.6, 2921.9, 2846.9, 1737.3, 1720.0, 1634.1, 1603.3, 1566.5, 1476.8, 1434.1, 1371.6, 1307.2, 1287.7, 1261.1, 1202.1, 1115.6, 1037.4 cm^{-1}; MS *m/z* (%): 359 (M^+, 12), 221 (35), 203 (100), 177 (16), 83 (25), 55 (26); HREIMS (*m/z*) calcd for $C_{21}H_{29}NO_4$ (M^+) 359.2097, found 359.2058.

2-Methoxy-6-oxo-5,6,7,8-tetrahydro-quinoline-5-carboxylic acid (1*S*)-1-*benzyloxycarbonyl-ethyl ester* (**4b**)

A mixture of **3** (118 mg, 0.5 mmol), benzyl (*S*)-lactate (450 mg, 2.5 mmol) and benzene (5 mL) was refluxed for 96 h. The cooled solution was concentrated and the residue was purified by flash column chromatography (using 1/10 ethyl acetate/petroleum ether as an eluent) to afford 13 mg (11%) of **3** and 167 mg (87%, or 98% based on 89% conversion) of **4b**.

4b $[\alpha]_D^{20}$ − 15.2 (*c* 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 12.81 (s, 1H), 8.04 (d, J = 8.7 Hz, 1H), 7.44—7.28 (m, 5H), 6.53 (d, J = 8.7 Hz, 1H), 5.41 (q, J = 7.0 Hz, 1H), 5.24 (s, 2H), 3.94 (s, 3H), 2.94 (m, 2H), 2.66 (m, 2H), 1.62 (d, J = 7.0 Hz, 3H); IR ν_{max}: 3411, 3034, 2957, 2921, 2837, 1753, 1640, 1600, 1566, 1477, 1434, 1376, 1352, 1321, 1300, 1264, 1200, 1115, 1094, 1037 cm^{-1}; MS *m/z* (%): 383 (M^+, 21), 292 (21), 203 (100), 177 (14), 91 (50); HREIMS (*m/z*) calcd for $C_{21}H_{21}NO_6$ (M^+) 383.1369, found 383.1324.

General procedure for chiral guanidine catalyzed reaction of **4** *and methacrolein*

To a mixture of **4** (0.1 mmol), guanidine **2** (0.02 mmol) in 2 mL of appropriate solvent was added methacrolein (0.16 mL, 2 mmol) at indicated temperature under nitrogen. The resultant mixture was stirred at the same temperature until the starting material disappeared monitored by TLC. After the reaction completed, the mixture was chromatographed eluting with 1/4 ethyl acetate/petroleum ether to afford the mixture **5**.

To a solution of the above alcohol **5**, triethylamine (0.14 mL, 1.0 mmol) and a catalytic amount of DMAP in 1.5 mL of dry CH_2Cl_2 was added mesyl chloride (0.03 mL, 0.4 mmol) at 0 ℃. After the resultant solution was stirred for 6 h at room temperature, it was partitioned between CH_2Cl_2 and saturated NH_4Cl. The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (using 1/2 ethyl acetate/petroleum ether as an eluent) to afford the corresponding mesylate, which was heated with anhydrous NaOAc (8 mg, 0.1 mmol) in AcOH (1 mL) at 120 ℃ under N_2 for 24 h. The acetic acid was removed by rotary evaporation. The residue was dissolved in ethyl ac-

As an extension of our program on the development of chiral guanidine-catalyzed reactions,[13] we investigated the Michael-aldol annulation of esters **4a** and **4b** derived from less expensive (-)-menthol and benzyl (*S*)-lactate using chiral guanidines as the catalysts. The results are detailed herein.

As outlined in Scheme 1, the known methyl ketoester (**3**) was prepared following the Kozikowski's procedure.[14] Transesterification of **3** with (-)-menthol or benzyl (*S*)-lactate in refluxing benzene afforded the corresponding ester **4a** or **4b** in excellent yield, respectively. With them in hand, we examined their bicycloannulation with methacrolein catalyzed by chiral guanidines **2a** to **2f** (Scheme 2). In order to determine the diastereoselectivity more easily, the annulation products **5a** and **5b** were further transformed into the olefins **6a** and **6b** by mesylation with mesyl chloride and the subsequent elimination mediated by NaOAc at 120 ℃. The stereochemistry of **6a** or **6b** was confirmed by hydrolyzing them to the known acid **7**.[8] The diastereomeric excess for product **6a** or **6b** was examined by their ^{1}H NMR data and in some cases was confirmed by HPLC analysis. The results are summarized in Table 1.

As shown in Table 1, the diastereoselectivity was highly dependent on the substrates and the chiral catalysts. Initially, reaction of **4a** with methacrolein catalyzed with 20 mmol% of the guanidine **2c** was selected as a model to examine the solvent effect. Among the five solvents we tested THF was found to give the best result (compare Entries 1—5). With THF as solvent and carrying out the reaction at room temperature, other guanidines were employed as the catalysts in order to improve the diastereoselectivity. However, only **2a** was slightly superior to **2c** (compare Entries 6—11). In addition, lower reaction temperature gave better diastereoselectivity (compare Entries 6 and 12).

Scheme 2

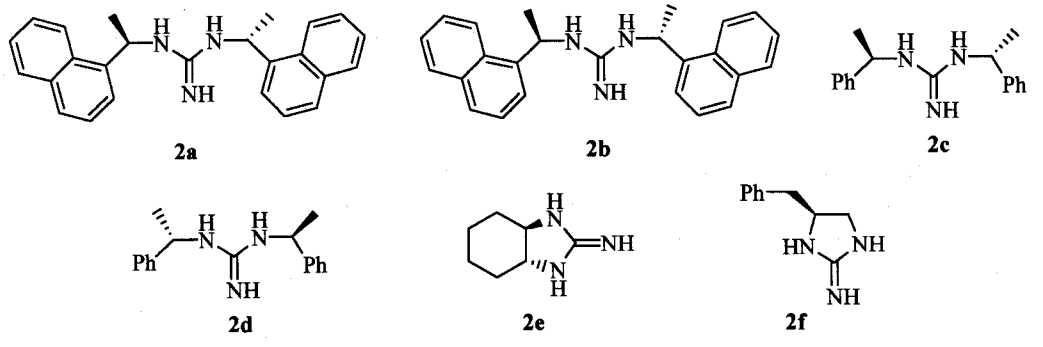

Table 1 Chiral guanidines catalyzed Michael-aldol annulation of **4** and methacrolein[a]

Entry	Substrate	Cat.	Solvent	Temperature (℃)	Time (h)	Yield of **5**[b] (%)	*de*[c] (%)
1	**4a**	**2c**	THF	0	36	96	28.6
2	**4a**	**2c**	CH_2Cl_2	0	36	92	9.1
3	**4a**	**2c**	$CHCl_3$	0	36	94	4.8
4	**4a**	**2c**	C_6H_6	0	36	91	13.0
5	**4a**	**2c**	CH_3CN	0	36	93	4.8
6	**4a**	**2a**	THF	25	24	94	24.7
7	**4a**	**2b**	THF	25	24	95	17.2
8	**4a**	**2c**	THF	25	24	96	17.7
9	**4a**	**2d**	THF	25	24	95	-5.7
10	**4a**	**2e**	THF	25	24	93	0.8
11	**4a**	**2f**	THF	25	24	92	6.8
12	**4a**	**2a**	THF	-20	48	86	39.9
13	**4b**	**2a**	THF	0	24	92	49.5
14	**4b**	**2b**	THF	0	24	90	41.8
15	**4b**	**2c**	THF	0	24	96	4.8
16	**4b**	**2d**	THF	0	24	96	52.1
17	**4b**	**2e**	THF	0	24	92	73.2
18	**4b**	**2f**	THF	0	24	92	60.4

[a] Reaction condition: **4** (0.1 mmol), methacrolein (2 mmol), guanidine **2** (0.02 mmol), solvent (2 mL). [b] Isolated yield. [c] The *de* values were determined by ^{1}H NMR spectra of **6**.

etate, washed with saturated Na_2CO_3 and brine, and dried. Evaporation of the solvent and flash chromatography of the residue (using 1/4 ethyl acetate/petroleum ether as an eluent) gave the product **6**.

6a (as a mixture of two inseparable isomers) of Entry 12 ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.13 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 8.6 Hz, 0.43H), 6.63 (d, J = 8.6 Hz, 0.43H), 6.59 (d, J = 8.6 Hz, 1H), 5.42 (m, 1.43H), 4.78 (m, 1.43H), 3.93 (s, 0.43H), 3.92 (s, 1H), 3.40 (m, 2.86H), 3.16 (m, 2.86H), 2.52 (d, J = 17.4 Hz, 1H), 2.49 (d, J = 17.4 Hz, 0.43H), 2.17—0.70 (m, 28.6H); IR ν_{max}: 3436.9, 2956.6, 2869.3, 1739.1, 1721.9, 1603.2, 1575.6, 1478.2, 1423.1, 1326.3, 1308.8, 1263.6, 1247.7, 1074.4, 1024.5 cm^{-1}; MS m/z (%): 411 (M^+, 7), 273 (40), 255 (100), 228 (22), 200 (45), 149 (56), 83 (64), 55 (58), 43 (62); HREIMS (m/z) calcd for $C_{25}H_{33}NO_4$(M^+) 411.2409, found 411.2364.

6b (two isomers are separable by column chromatograpgy) Major isomer: $[\alpha]_D^{20}$ + 48.4 (c 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.40—7.34 (m, 5H), 7.28 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 8.6 Hz, 1H), 5.44 (m, 1H), 5.27 (q, J = 7.1 Hz, 1H), 5.17 (dd, J = 12.2, 23.6 Hz, 2H), 3.91 (s, 3H), 3.38 (m, 1H), 2.18 (m, 1H), 2.48 (d, J = 17.4 Hz, 1H), 1.61 (s, 3H), 1.41 (d, J = 7.1 Hz, 3H); IR ν_{max}: 3465.4, 2939.8, 1746.4, 1601.8, 1575.5, 1478.6, 1424.5, 1378.0, 1326.3, 1260.3, 1243.0, 1193.7, 1098.1 cm^{-1}; MS m/z (%): 435 (M^+, 8), 316 (31), 255 (23), 200 (48), 184 (20), 91 (100), 43 (23); HREIMS (m/z) calcd for $C_{25}H_{25}NO_6$(M^+) 435.1682, found 435.1641. Minor isomer: $[\alpha]_D^{20}$ - 8.9 (c 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.37—7.34 (m, 5H), 7.20 (d, J = 8.6 Hz, 1H), 6.54 (d, J = 8.6 Hz, 1H), 5.43 (m, 1H), 5.30 (q, J = 7.1 Hz, 1H), 5.22 (dd, J = 12.2, 23.6 Hz, 2H), 3.90 (s, 3H), 3.39 (m, 1H), 2.16 (m, 1H), 2.58 (d, J = 17.4 Hz, 1H), 1.61 (s, 3H), 1.44 (d, J = 7.1 Hz, 3H); IR ν_{max}: 3463.8, 2934.0, 1747.7, 1601.4, 1577.0, 1478.6, 1424.2, 1326.0, 1261.3, 1238.6, 1097.0, 1029.2 cm^{-1}; MS m/z (%): 435 (M^+, 11), 316 (23), 255 (16), 200 (58), 184 (17), 91 (100), 43 (18); HREIMS (m/z) calcd for $C_{25}H_{25}NO_6$(M^+) 435.1682, found 435.1672.

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