Approach to synthesis of novel chiral 3-chloro-2(5H)-furanone and its application in asymmetric reactions

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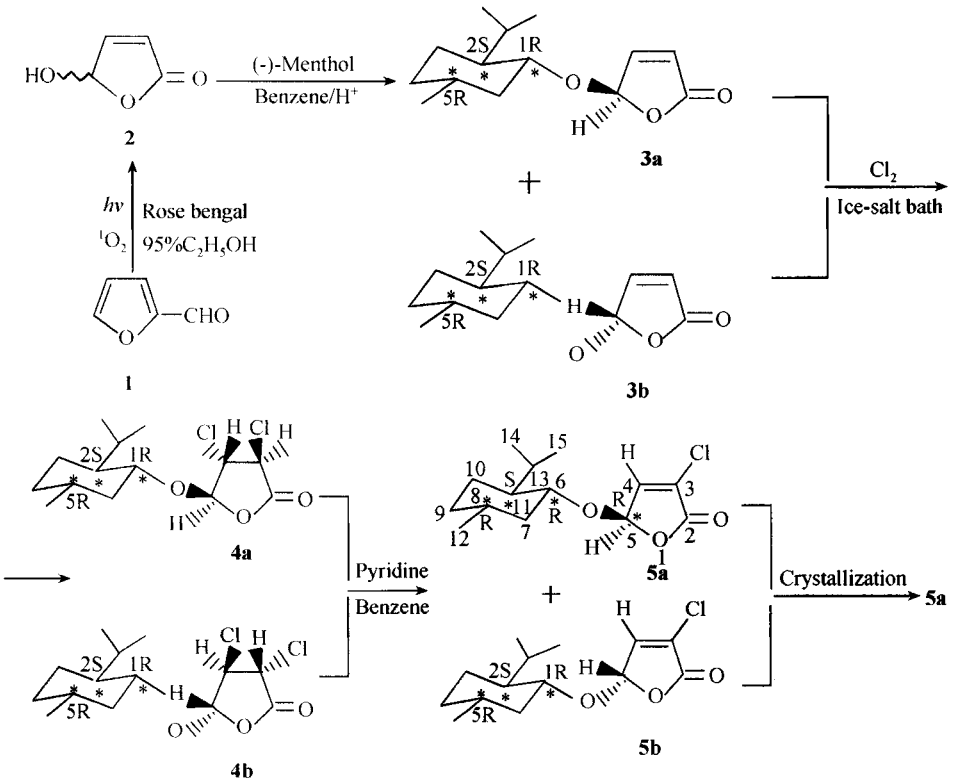
Abstract The synthetic method of the novel chiral synthon, 5-*l*-menthyloxy-3-chloro-2-(5H)-furanone **5a** and its application in asymmetric reactions were investigated. **5a** is easily obtained in highly optical purity, and acts as a stable acceptor of Michael addition with oxygen nucleophiles in tandem double Michael addition / internal nucleophilic substitution to offer the spiro-cyclopropane derivative containing four stereogenic centers **8**, which it is difficult to obtain by routine methods. The synthetic methods for **5a** and **8** are reported in detail and the new compounds are identified on the basis of their analytical data and spectroscopic data, such as UV, IR, ^{1}H NMR, ^{13}C NMR, MS and elementary analysis. The absolute configuration of the interesting spiro-cyclopropanes, spiro [1-chloro-4-(*l*-menthyloxy)-5-oxo-6-oxa-biscyclo[3.1.0]hexane-2,3′-(4′-*l*-menthyloxy-5′-*l*-menthyloxy-

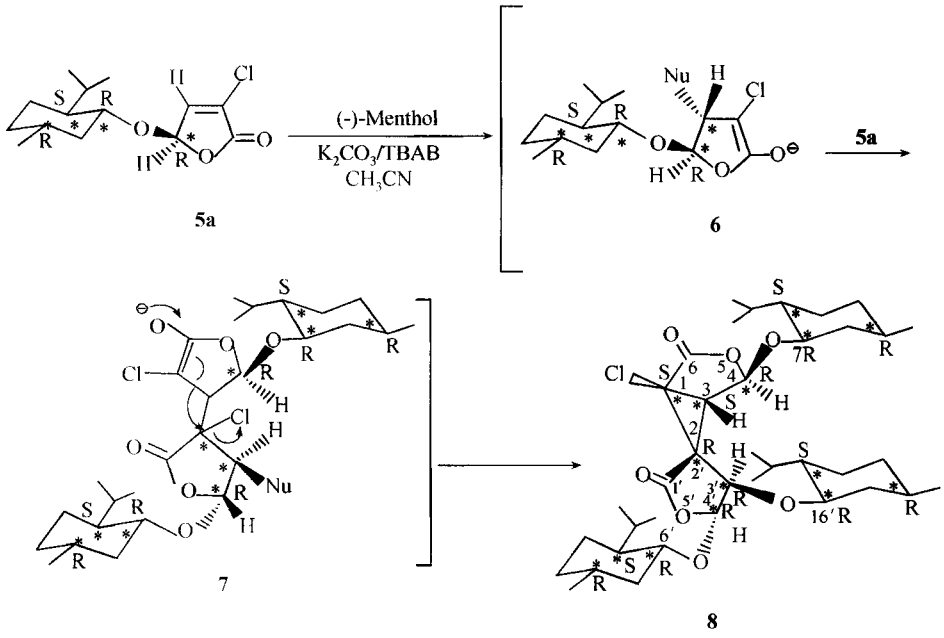
butyrolactone)] **8** was established by X-ray crystallography. This result can provide important synthetic strategy in synthesis of some complex molecules containing spiro-cyclopropane skeleton with multiple chiral centers.

Keywords: new chiral synthon, 5-*l*-menthyloxy-3-chloro-2-(5H)-furanone, absolute configuration, spiro-cyclopropane derivative containing multiple chiral centers.

Synthesis of new chiral synthons and their application in synthesis for complex molecules and natural products are an extremely active field in organic chemistry[1−5]. On the basis of the previous works[2−11], we have deeply studied the synthetic method of the novel chiral synthon, 5-(*R*)-[*l*-(-)-menthyloxy]]-3-chloro-2(5H)-furanone **5a** and its application in asymmetric reaction. Through the photooxidation of furfural **1** 5-hydroxy-2(5H)-furanone **2** is conveniently obtained and then the epimeric mixture of 5-menthyloxy-2(5H)-furonone **3a+3b** is readily available by acetalization of **2** with (-)-menthol. The preparation of enantiomerically pure **5a** is based on the recrystallization of epimeric mixture of **5a+5b** which is obtained directly from the chloronation of epimeric mixture of **3** followed by the elimination of hydrogen bromide of the adducts **4a+4b**. The chiral synthon **5a** is not only easily obtained in its preparation but also in its single optical purity. Moreover, the 3-chloro-2(5H)-furanone **5a** behave as a stable Michael acceptors towards carbon, oxygen, sulfur and nitrogen nucleophiles to give enantiomerically pure spiro-cyclopropane derivatives containing multiple chiral centers **8** which is difficult to obtain by routine methods, e.g. via tandem double Michael addition/internal nucleophilic substitution. This synthetic method can provide important synthetic strategy in synthesis of some complex structure compounds containing spiro-cyclopropane skeleton with multiple chiral centers. We would like to report in detail the synthesis of **5a** and **8**, as well as their spectroscopic data and crystal structure. The synthetic routes are shown in scheme 1 and scheme 2.



Scheme 1. Synthetic route to chiral 3-chloro-2(5H)-furanone **5a**.



Scheme 2. Synthetic route to spiro-cyclopropane bisbutyrolactones **8**.

1 Experimental

(i) General methods. Yanaco/mp-50b melting point apparatus (uncorrected), Shimazu UV-760 ultraviolet absorption detector, 170-5x-Fourier infrared spectrometer, Varian Unity 200 MHz and Broker DMX-300 Nuclear Magnetic Resonance spectrometer (TMS as internal standard), Kykyqp-1000A Mass spectrometer and Micro-Mass Zabspec spectrometer, Perkin-Elmer 241-C polarimeter and Perkin-Elmer 240-C elementary analyzer were used. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with an evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate-petroleum ether (30—60℃) mixture as the eluent. The organic extracts were dried over anhydrous magnesium sulfate. All reagents were of reagent grade and purified where necessary.

(ii) 5-(R)-(*l*-Menthyloxy)-3-chloro-2(5H)-furanone **5a**. A solution of **3a**+**3b** (30 g, 0.129 mol) in CCl_4 (200 mL) was at ice-salt temperature, to which was passed slowly chlorine (10 g, 0.14 mol). The reaction mixture was stirred at room temperature at which the epimeric mixture **3a**+**3b** was consumed as monitored by TLC. The stirring was continued at 0℃ on an ice bath while pyridine (20 mL, 0.25 mol) was dropped slowly. The whole mixture was stirred at the same temperature for 2 h, and then filtered. The organic layer was washed with brine to remove the pyridine salt and the solvent was removed in vacuum. The epimeric mixture **5a**+**5b** as a brown-yellow solid was obtained. The epimeric mixture **5a**+**5b** was checked by ^{1}H NMR analysis, **5a**:**5b** = 6:4, $\delta_{5a}(CCl_4)$ = 6.06 (0.6H, s, H-**5a**); $\delta_{5b}(CCl_4)$ = 5.85 (0.4H, s, H-**5b**). Enantiomerically pure **5a** as pale yellow crystals was obtained after 2 —3 crystallizations from petroleum ether (30—60℃). ^{1}H NMR spectra showed a single epimer **5a**, $\delta_{5a}(CCl_4)$=5.97 (1H, s, H-**5a**) and lost the characteristic shift of **5b**. The mother liquors were evaporated and the residue was crystallized 2—3 times from petroleum ether as described above to afford additional enantiomerically pure **5a**. **5a**: 13.4 g (combined yield 38%), d.e.≥98%; as a pale yellow crystal. m.p. 81—82℃ (from petroleum ether); $[\alpha]_D^{20}$ = −144.4 (c 1.57, $CHCl_3$); UV (λ_{max}, $CHCl_3$), 247.0 (lgε 2.252) nm; IR (KBr, cm^{-1}): 2 922, 2 857 (CH), 1 779 (C=O), 1 627 (C=C), 1 153 (COC

Vas), 919 (COC,Vs); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.80 (3H, d, J = 7.2 Hz, 3H-12), 0.90 (3H, d, J = 6.8 Hz, 3H-14), 0.99 (3H, d, J= 6.8 Hz, 3H-15), 1.24 (2H, m, 2H-10), 1.42 (2H, m, 2H-9), 1.70 (2H, m, 2H-7), 2.13 (3H, m, H-8, H-11, H-13), 3.68 (1H, bt, J=10.8, 10.8, 4.6 Hz, H-6), 6.06 (1H, s, H-5), 7.04 (1H, s, H-4) ppm. ^{13}C NMR (45 MHz, $CDCl_3$) δ: 15.6 (C-15), 20.8 (C-14), 22.1 (C-12), 22.9 (C-10), 25.1 (C-13), 31.4 (C-8), 34.0 (C-9), 40.1(C-7), 47.6(C-11), 79.3 (C-6), 98.3 (C-5), 128.8 (C-4), 142.5 (C-3), 165.5 (C-2) ppm; EIMS m/z: 273 (M^+ +1, 14), 236 (M^+-Cl, 14), 95 ($C_7H_{11}^+$, 15), 29($C_2H_5^+$, 65), 28 ($CO^{+\cdot}$, 100); Anal. calcd for $C_{14}H_{21}O_3C_l$: C, 61.65, H, 7.76; found: C, 61.26, H, 7.92).

(iii) Spiro[1-chloro-4-(*l*-menthyloxy)-5-oxo-6-oxa-biscyclo-[3.1.0] hexane-2,3′-(4′-*l*-menthyloxy -5′-*l*-menthyloxy butyrolactone)] **8**. (-)-Menthol (1.09 g, 7 mmol) under a N_2 atmosphere was added to the mixture of powdered K_2CO_3 (1.11g, 8 mmol), tetrabutyl ammonium bromide (0.32 g, 1 mmol) and acetonitrile (6 mL). The mixture was stirred for 20 min. Then, chiral synthon (0.55 g, 2 mmol) **5a** was added and the mixture was stirred at room temperature for 3 d, at which **5a** was consumed as monitored by TLC. After the addition of acetonitrile (50 mL), the mixture was filtered and the salts were washed with acetonitrile. The organic layer was dried and evaporated under reduced pressure, and the residue (1.8 g) was purified by flash chromatography (petroleum ether/ethyl acetate was 98:2) yelding **8** (0.14 g, 21%) as a white crystal: R_f 0.34 (6.4 % EtOAc-petroleum ether, 30—60℃); m. p. 58.5—60.1℃ (from petroleum ether, 30—60℃); $[\alpha]_D^{20}$ = −180.2 (c 0.56, $CHCl_3$); UV (λ_{max}, 95% C_2H_5OH): 217.2 (lgε 2.811) nm; IR (KBr, cm^{-1}): 3 070(C-H), 1 800(C=O), 1 138(COC, Vas), 9 26(COC, Vs); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.70 (3H, d, J=7.0 Hz, CH_3), 0.75 (3H, d, J=6.8Hz, CH_3), 0.78 (3H, d, J=6.8 Hz, CH_3), 0.84 (3H, d, J=7.2 Hz, CH_3), 0.87 (3H, d, J=6.8 Hz, CH_3), 0.90 (3H, d, J=6.8 Hz, CH_3), 0.92 (3H, d, J=7.0 Hz, CH_3), 0.95 (3H, d, J=6.8 Hz, CH_3), 0.96 (3H, d, J=6.80 Hz, CH_3), 1.16—1.56 (10H, m, 5×CH_2), 1.58—1.72 (8H, m, 6×CH_2), 2.07—2.23 (8H, m, 8×CH), 3.25 (1H, s, 4-H), 3.45 (1H, bt, J=10.8, 10.8, 4.60 Hz, 16′-OCH), 3.56 (2H, bt, J=10.8, 10.8, 4.6 Hz, 6′-H, 7-H), 3.65 (1H, s, 4′-H), 5.61 (1H, s, 5′-H), 5.73 (1H, s, 5-H); ^{13}C NMR (45 MHz, $CDCl_3$) δ: 15.9, 16.1, 16.2, 21.1, 21.3, 21.8, 22.3, 22.4, 22.5, 23.3, 23.5, 23.9, 25.5, 25.7, 26.3, 30.7, 30.8, 32.0, 32.1, 32.2, 34.7, 34.8, 34.9, 38.5, 40.3, 40.7, 43.4, 48.3, 48.4, 48.5, 48.9, 77.7, 79.7, 81.1, 98.2, 103.7, 167.9, 169.1 ppm; FAB m/z: 664 (M^+, 6), 527(M^+ $C_{10}H_{17}^+$, 47), 139 ($C_{10}H_{19}^+$, 89), 83 ($C_4H_3O_2^+$, 100); Anal. calcd for $C_{38}H_{61}O_7Cl$: C, 68.60; H, 9.24; found: C, 69.02; H, 9.59.

Preparation of crystal: **8** was dissolved in ethyl acetate-petroleum (30—60℃). A colorless monocrystal was separated out from solution at room temperature after standing for several days. X-ray crystallography: 0.15 mm×0.1 mm×0.1 mm colorless monocrystal of chiral compound **8**, $C_{38}H_{61}O_7Cl$, M_r 665.3. Crystal **8** is attributed to orthorhombic system and $P\,2_12_12_1$ space group. The crystal lattice parameters are a = 1.262 2(3) nm, b = 2.899 9(6) nm, c = 1.064 4(2) nm, V = 3.896(2) nm^3, Z = 4, D_c = 1.134 g/cm^{-1}, μ = 0.142 mm^{-1}, F(000) = 1 448. It was determined on a Rigaku AFC6S P_4/PC X-ray diffratormeter with the incident radiation of MoKα ray (λ=0.071 073 nm), which was monochromalized by graphite. 3 869 diffraction points of diffraction intensity ($2\theta_{max}$=50) were collected at R.T.(21±1)℃ with ω-θ scanning pattern, in which there were 3 869 absolute diffraction points and 1 391 perceivable points of $I \geqslant 2\sigma(I)$. The rectified results of nonhydrogen atom coordinates and their thermoparameters of aeolotropism by the least squares method are: the deflection factor [$F^2>2\sigma(F^2)$], R = 0.069 7, R_w = 0.091 4, the maximum residual peak in the D-value Fourier scheme is 0.28×10^2 e • nm^{-3}. All were calculated and rectified with Siemens SHELXTL program.

2 Results and discussion

The asymmetric reaction of novel chiral reagent **5a** with nucleophilic reagent, (-)-menthol has been studied in this note. 5-(*l*-Menthyloxy)-3-chloro-2(5H)-furanone **5a** possesses unique structure character that determines its control of stereoselectivity. The tandem asymmetric double-Michael addition/internal nucleophilic substitution reaction of **5a** with (-)-menthol as an oxygen nucleophilic reagent in acetonitrile at room temperature, in the presence of dehydrated powder K_2CO_3 as basic media and tetrabutyl ammonium bromide (TBAB) as phase transfer catalyst, afforded optically pure

spiro[1-chloro-4-(*l*-menthyloxy)-5-oxo-6-oxa-biscyclo[3.1.0]hexane-2,3′-(4′-*l*-menthyloxy-5′-*l*–menthy-loxybutyrolactone)] containing four stereogenic centers **8** (scheme 2). The behavior of the 5-(*R*)-[(1*R*, 2*S*, 5*R*)-(-)-menthyloxy]-3-bromo-2(5H)-furanone **5a** could be explained on the basis of a reaction mechanism of the racemic 5-methoxy-3-bromo-2(5H)-furanone[12], in which the chiral 3-bromo furanone **5a** reacts readily with nucleophiles to give the Michael adducts. When an anion, such as a carbanion, is used as a nucleophile, the carbanionic intermediate of type **6**, in the absence of a proton donor, adds to a second molecule of the chlorofuranone **5a** to give a new anionic intermediate, the enolate anion **7**. This intermediate, at room temperature, suffers an internal nucleophilic substitution of the halogen to yield the optically active spiro-cyclopropane bisbutyrolactones **8**. The orientation temperature plot (ORTEP) drawing of **8** is shown in fig.1. Because the absolute configuration of (1*R*, 2*S*, 5*R*)-(-)-menthyloxy is unchanged during the asymmetric reaction process, the absolute configuration of **8** at the new stereogenic centers was established as 1(*S*), 2(*R*), 3(*S*), 3′(*R*). Moreover, the two chiral centers , C-4(R) and 4′(R), come from C-5 of the original chiral synthon **5a**, in which the absolute configuration is also unchanged during the asymmetric reaction process, and therefore the absolute configuration at the acetal carbon C-5 of **5a** is proven to be *R* by X-ray crystallography. At present, we have further studied the tandem asymmetric Michael addition/internal nucleophilic substitution reaction of the chiral synthon **5a** with various carbon, oxygen, sulfur and nitrogen nucleophiles and have obtained some chiral spiro/cyclopropane compounds. These results provided a

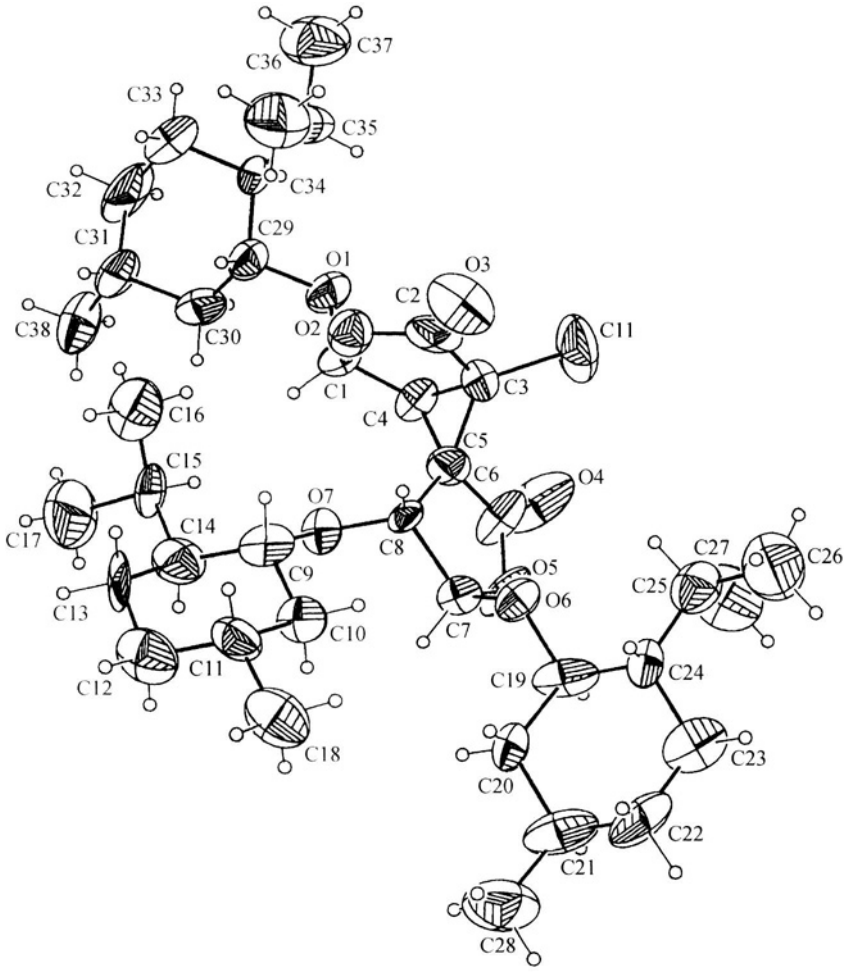


Fig. 1. The ORTEP drawing of the molecule of **5a**.

valuable synthetic route to potentially interesting enantiomerically pure spiro-cyclopropane compounds. The purpose of the present study is to propose the groundwork for future applications of the interesting tandem asymmetric reaction to the synthesis of more complex molecules containing similar spiro-cyclopropane skeleton.

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