Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1295–1307

TETRAHEDRON: *ASYMMETRY*

A valuable synthetic route to spiro-cyclopropane derivatives containing multiple stereogenic centers

Hui Huang † and Qinghua Chen *

Department of Chemistry, Beijing Normal University, Beijing 100875, People's Republic of China

Received 1 March 1999; accepted 23 March 1999

Abstract

The unusual, functionalized spiro-cyclopropane derivatives containing four stereogenic centers **8a**–**8f** were obtained in good yields with d.e. ≥98% via tandem double Michael addition/internal nucleophilic substitution of the novel chiral synthon, 5-*l*-menthyloxy-3-bromo-2(5*H*)-furanone **5a**, with various oxygen nucleophiles under mild conditions. (*S*)-(−)-Ethyl lactate also reacted under the same conditions to afford the corresponding spiro-cyclopropane derivative **8g**. Interestingly, reaction of **5a** with ethyl bromo- and chloroacetate, in the usual manner, gave the spiro-cyclopropane **8h** rather than the expected C-linked derivative. The absolute configuration of the interesting spiro-cyclopropanes **8** was established by X-ray crystallography. These results provide a valuable synthetic route to some complex molecules containing the spiro-cyclopropane skeleton with multiple stereogenic centers.

1. Introduction

We recently reported[1] our preliminary results on the synthesis of enantiomerically pure spiro-cyclopropane derivatives containing multiple stereogenic centers. In this article, we provide full details of both the preparation of chiral synthon 5-(*R*)-[(1*R*,2*S*,5*R*)-menthyloxy]-3-bromo-2(5*H*)-furanone **5a** and its X-ray single crystal structure, and a valuable synthetic route to the novel functionalized spiro-cyclopropane derivatives containing four stereogenic centers **8a**–**8f**. The chiral synthons obtained from natural chiral auxiliaries, such as (1*R*,2*S*,5*R*)-(−)-menthol and *endo*-(1*S*)-borneol, have recently become a topic of growing interest in the asymmetric synthesis of some biologically active compounds.[2,3] The 5-alkyloxy-2(5*H*)-furanones behave as Michael acceptors towards carbon, oxygen, sulfur and nitrogen nucleophiles to give 5-alkyloxy-4-substituted-butyrolactones.[4–6a] However, the 5-(*l*-menthyloxy)-3,4-dihalo(chloro or bromo)-2(5*H*)-furanone reacts readily with nitrogen and sulfur nucleophiles to

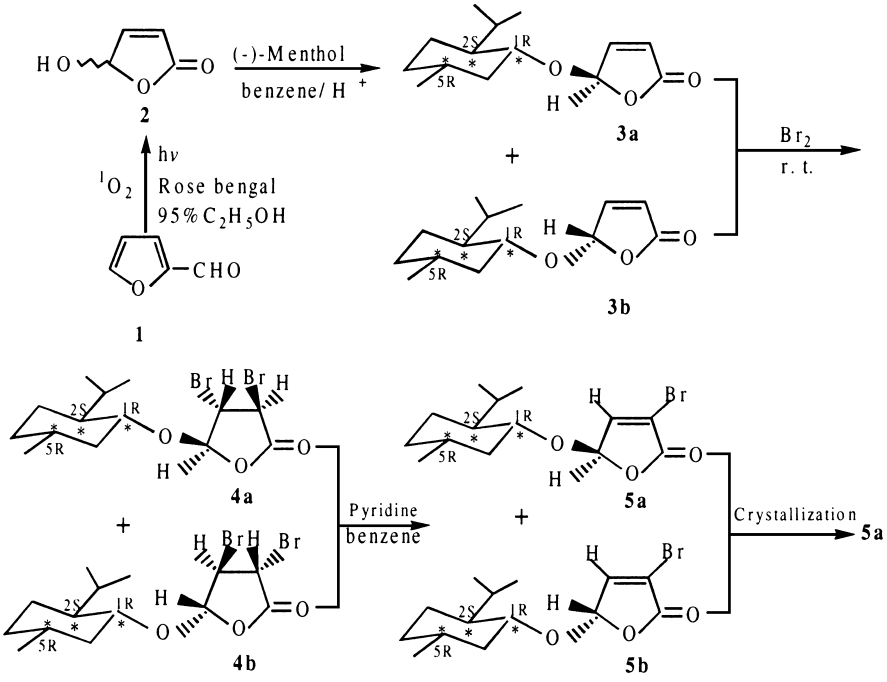
* Corresponding author. Tel: (86) 010-6220-7843; fax: (86) 010-6220-0567; e-mail: qinghuac@bnu.edu.cn

† Visiting scholar, Department of Chemistry, Tonghua Teacher's College, Tonghua, 134002, Jilin, People's Republic of China.

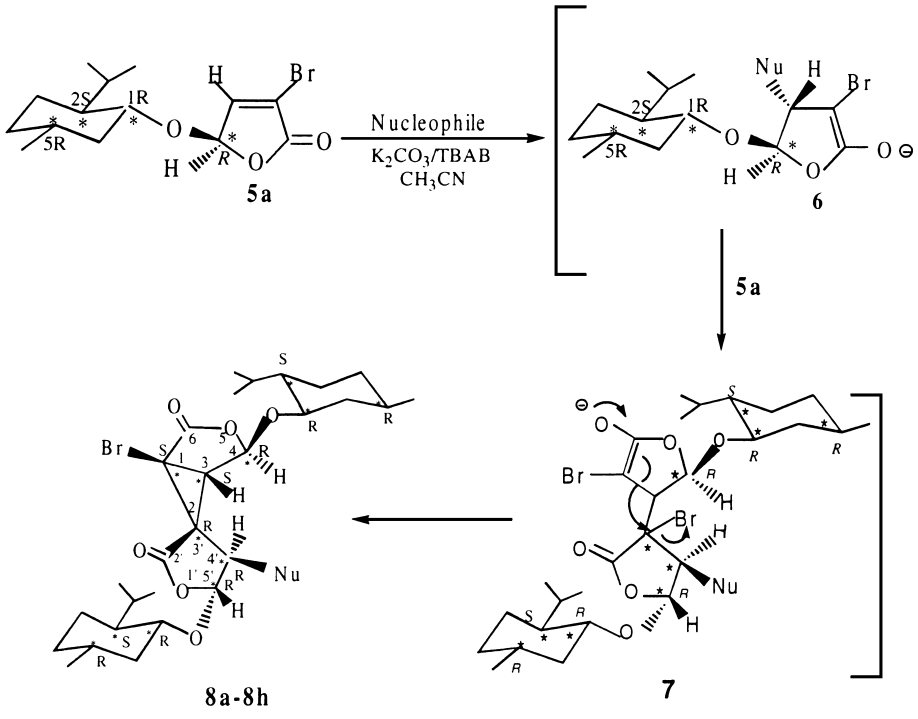
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00123-8

give the tandem Michael addition/elimination products, 5-(*l*-menthyloxy)-4-substituted-3-halo-2(5*H*)-furanones.[6b–e]

We have recently successfully synthesized the novel chiral synthon 5-(*R*)-[(1*R*,2*S*,5*R*)-menthyloxy]-3-bromo-2(5*H*)-furanone **5a**, which was obtained in 46% yield with d.e. ≥98%, from the epimeric mixture of 5-(*l*-menthyloxy)-3-bromo-2(5*H*)-furanone via bromination of the epimeric mixture of 5-(*l*-menthyloxy)-2(5*H*)-furanone, followed by the elimination of hydrogen bromide (Scheme 1). After recrystallization of the epimeric mixture, the enantiomerically pure **5a** was obtained as pale yellow needles, mp 89–90°C (petroleum ether, 30–60°C).[1] On the basis of previous work, we have accomplished the tandem asymmetric double Michael addition/internal nucleophilic substitution of **5a** with new oxygen nucleophiles such as biphenyl methanol, benzyl alcohol, (±)-α-methyl benzyl alcohol, *l*-menthol, *endo*-(1*S*)-borneol and cycloheptanol, in acetonitrile at room temperature, in the presence of potassium carbonate and tetrabutylammonium bromide as a phase transfer catalyst. The enantiomerically pure compounds, spiro-cyclopropane bisbutyrolactones **8a**–**8f**, with four stereogenic centers were obtained in 58–88% yields with d.e. ≥98% by the tandem asymmetric reaction under mild conditions (Scheme 2). (*S*)-(−)-Ethyl lactate also reacts in the usual manner to give **8g**. Interestingly, reaction of **5a** with ethyl bromo- and chloroacetate, using the above reaction conditions, afforded the spiro-cyclopropane **8h** rather than the expected C-linked derivative. The formation of the spiro-cyclopropane derivatives containing four stereogenic centers **8a**–**8h** via tandem double Michael addition/internal nucleophilic substitution is listed in Table 1. These results provide a valuable synthetic route to potentially interesting enantiomerically pure spiro-cyclopropane compounds. The aim of the present study would be to propose further groundwork for any future applications on the interesting tandem asymmetric reaction to the synthesis of more complex molecules containing similar spiro-cyclopropane skeleton.



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



Scheme 2. Synthetic route to spiro-cyclopropane derivatives containing multiple chiral centers **8a**–**8h**

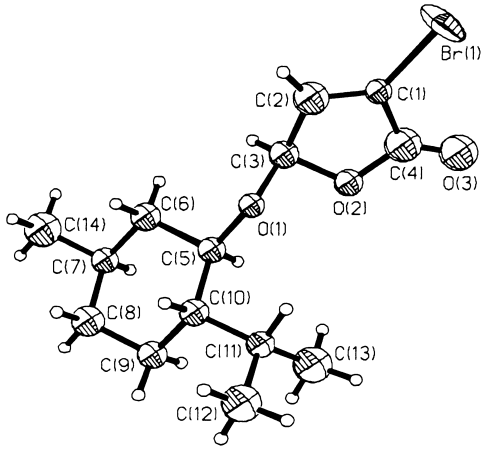


Figure 1. ORTEP drawing of the molecule **5a**

Table 1
Formation of the spiro-cyclopropane derivatives containing four stereogenic centers **8a**–**8h** via tandem double Michael addition/internal nucleophilic substitution

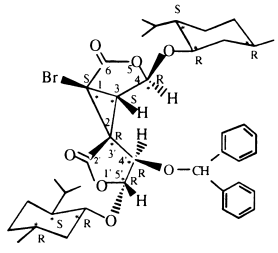
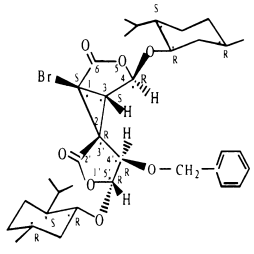
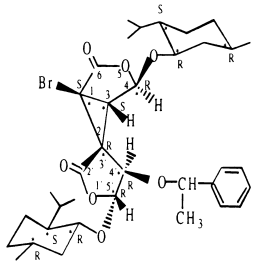
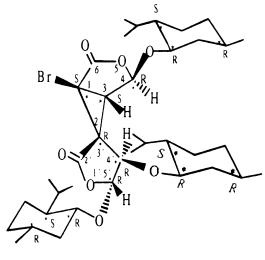
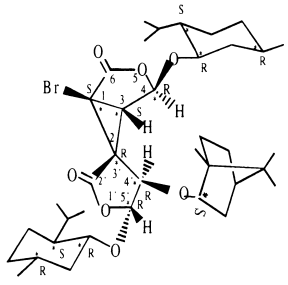
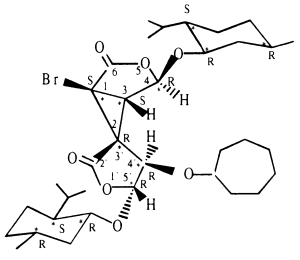
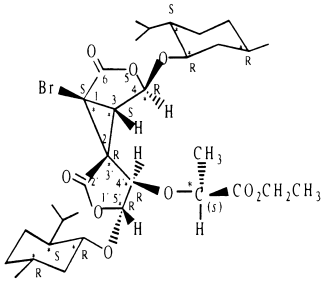
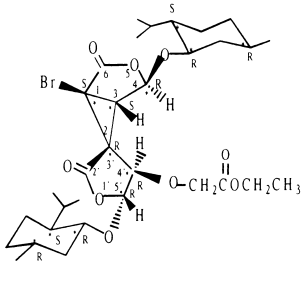
entries	nucleophile	mmol ratio **5a** /nucleophile	reaction time, day	product (% isolated yield)
1	Ph_2CHOH	2 / 7	1	 **8a** (84)
2	$PhCH_2OH$	2 / 7	1	 **8b** (70)
3	$PhCH(CH_3)OH$	2 / 7	1	 **8c** (62)
4	(*l*)- (-)-Menthol	2 / 7	9	 **8d** (58)

Table 1 (continued)

5	endo-(1*S*)-Borneol	2 / 7	6	 **8e** (64)
6	Cycloheptanol	2 / 7	4	 **8f** (68)
7	(*S*)-Ethyl lactate	2 / 4	10	 **8g** (49)
8	Ethyl bromoacetate	2 / 4	12	 **8h** (37)

2. Results and discussion

The synthesis of enantiomerically pure 5-*l*-menthyloxy-3-bromo-2(5*H*)-furanone **5a** is conveniently achieved starting from 5-hydroxy-2(5*H*)-furanone **2**. The photooxidation of furfural **1** is probably most suitable in the preparation of **2**.[4b,6a,g,7] We have performed the improved photosynthetic procedure using 95% C_2H_5OH as a solvent at room temperature providing 5-hydroxy-2(5*H*)-furanone in good yield.[8] Epimeric mixtures of the 5-menthyloxy-2(5*H*)-furanone **3** are readily available through acetalization of the resulting 5-hydroxy-2(5*H*)-furanone with (−)-menthol in refluxing benzene in the presence of a catalytic amount of condensed sulfuric acid.[6,8] Preparation of enantiomerically pure **5a** is based on the recrystallization of the epimeric mixture of 5-menthyloxy-3-bromo-2(5*H*)-furanone **5** which is obtained directly from the bromination of the epimeric mixture of **3** followed by the elimination of hydrogen bromide. The furanone **5a** was identified on the basis of its satisfactory elemental analytical and spectroscopic data. Examination of the X-ray structure of **5a** (Fig. 1) led to the important conclusion that the absolute configuration at the acetal carbon of **5a** proved to be *R*.[9]

The spiro-cyclopropane bisbutyrolactones **8a**–**8f** were identified on the basis of their analytical and spectroscopic data. The absolute configuration of the chiral spiro-cyclopropane bisbutyrolactone **8a** was established by X-ray crystallography and spectroscopic analysis. The presence of two 5-menthyloxy-2(5*H*)-furanone moieties was deduced from the ^{1}H NMR spectrum, which showed two signals at δ: 5.20 (1H, s, H-5′) and 5.50 (1H, s, H-4) assignable to the acetal protons. In addition, the ^{1}H NMR spectrum showed two signals at δ: 3.05 (1H, s, H-3) and 3.86 (1H, s, H-4′), where there was an absence of coupling constants between the vicinal protons H-3/H-4 and H-4′/H-5′, established a *trans* relationship. The presence of an IR band at 3066 cm^{-1} was assignable to a C–H stretch in a cyclopropane ring, and the signal at δ: 38.28 (C-3) ppm of the ^{13}C NMR spectrum was also in agreement with the presence of a cyclopropane ring. On the basis of the data, the proposed structure of spiro-cyclopropane bisbutyrolactone **8a** was consistent with the stereochemistry of the molecule **8a**, and this was further validated by its X-ray structural analysis.[9]

The ORTEP drawing of **8a** is shown in Fig. 2. Because the absolute configuration of the (1*R*,2*S*,5*R*)-menthyloxy moiety is unchanged during the asymmetric reaction process, the absolute configuration of **8a** at the new stereogenic centers was established as 1(*S*),2(*R*),3(*S*),4′(*R*). The bond angles of the cyclopropane moiety of **8a** are approximately 60° and agree with theory values of the internal angles in a cyclopropane (∠θ C(3)–C(1)–C(2)=62.0(9)°; ∠θ C(1)–C(3)–C(2)=59.9(9)°; ∠θ C(1)–C(2)–C(3)=58.1(9)°).

We have further investigated the reaction of the chiral synthon **5a** with (*S*)-ethyl lactate, which indeed afforded the expected spiro-cyclopropane derivative **8g**. The structure of **8g** was established on the basis of its analytical and spectroscopic data and by X-ray crystallography.[9] The ORTEP drawing of **8g** is shown in Fig. 3. The absolute configuration of the (1*R*,2*S*,5*R*)-menthyloxy and (*S*)-(−)-ethyl lactate groups remained unchanged during the asymmetric reaction process, and the absolute configuration of **8g** at the new stereogenic centers was established as 1(*S*),2(*R*),3(*S*),4′(*R*). In view of this interesting result, the tandem asymmetric reaction of the 5-(*R*)-(*l*-menthyloxy)-3-bromo-2(5*H*)-furanone **5a** with ethyl bromo- and chloroacetate under the mentioned reaction conditions afforded the same product, spiro-cyclopropane bisbutyrolactone **8h**, which possesses the $EtO_2C–CH_2O–$ group instead of the expected $EtO_2C–CHX–$ group. The structure of **8h** was established on the basis of its analytical and spectroscopic data, such as UV, IR, ^{1}H NMR, ^{13}C NMR, MS and elementary analysis. In particular, the ^{1}H NMR spectrum showed the two signals at δ: 4.13 (2H, d, *J*=15.9 Hz) and δ: 4.33 (2H, q, *J*=7.2 Hz) assignable to the protons, respectively, in $–O–CH_2–CO_2CH_2CH_3$. In addition, two signals at δ: 3.19 (1H, s) and 3.77 (1H, s), where there was an absence of coupling constants between the vicinal protons H-3/H-4 and H-4′/H-5′, established a *trans* relationship. The two signals at δ: 5.89 (1H, s) and 6.20 (1H, s) were

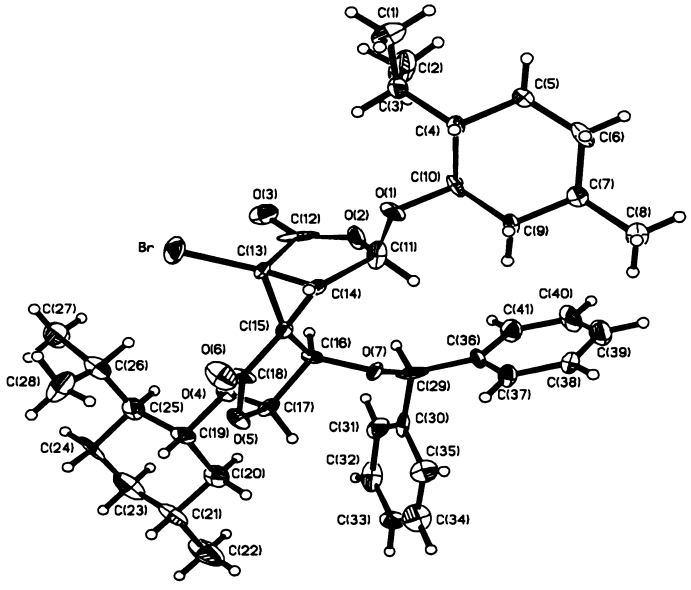


Figure 2. ORTEP drawing of the molecule **8a**

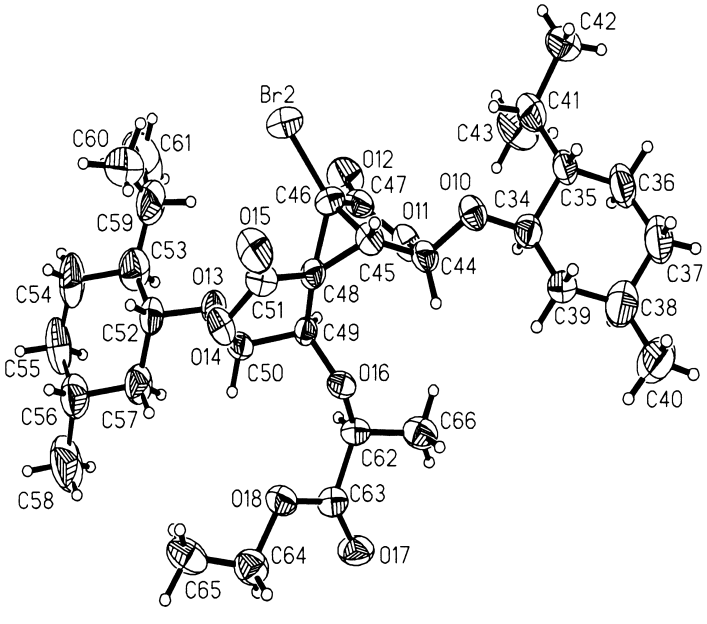


Figure 3. ORTEP drawing of the molecule **8g**

assignable to the acetal protons. The presence of an IR band at 3070 cm^{-1} was assignable to a C–H stretch in a cyclopropane ring and the signal at δ: 38.66 (C-3) ppm of the ^{13}C NMR spectrum was also in agreement with the presence of a cyclopropane ring. These results indicate that the reaction proceeds after previous displacement of the halogen by the hydroxy group, the corresponding alkoxide being the anionic species that initiates the Michael addition.[5a]

The behavior of the 5-(*R*)-[(1*R*,2*S*,5*R*)-menthyloxy]-3-bromo-2(5*H*)-furanone **5a** could be explained on the basis of a reaction mechanism of the racemic 5-methoxy-3-bromo-2(5*H*)-furanone,[5a] 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 nucleophilic, the carbanionic intermediate of type **6**, in the absence of a proton donor, adds to a second molecule of the bromofuranone **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 **8a**–**8h**.

3. Conclusion

The synthesis of potentially interesting enantiomerically pure spiro-cyclopropane derivatives was accomplished using an asymmetric tandem double Michael addition/internal nucleophilic substitution of the chiral synthon, 5-(*l*-menthyloxy)-3-bromo-2(5*H*)-furanone, with various oxygen nucleophiles. The stereochemical structure and absolute configuration of the cyclopropane derivatives were established by X-ray crystallography. Moreover, this work demonstrates the asymmetric reaction of ethyl bromo- and chloroacetate with the chiron **5a** under the same conditions to afford spiro-cyclopropane **8h** rather then the expected C-linked derivative. At present, we have studied the removal of the chiral auxiliary (menthyloxy group) from the spiro-cyclopropanes and the asymmetric reactions of the chiral synthon with different series of nucleophilic reagents such as carbon, oxygen, nitrogen and sulfur nucleophiles. The application of this synthetic strategy to generate potentially interesting enantiomerically pure spiro-cyclopropane derivatives in asymmetric synthesis is currently ongoing and will be reported in due course.

4. Experimental

4.1. General

Yanaco/mp-50b melting point apparatus (uncorrected); Shimadzu UV-760 ultraviolet absorption detector; 170-5x-Fourier infrared spectrometer; Varian Unity 200 MHz and Bruker DMX-300 nuclear magnetic resonance spectrometers (TMS as internal standard); Kykyqp-1000A mass spectrometer and Micro-Mass Zabspec spectrometer; Perkin–Elmer 241-C polarimeter; Perkin–Elmer 240-C elementary analyzer; 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 mixture (30–60°C) as the eluent. The organic extracts were dried over anhydrous magnesium sulfate. All reagents were of a reagent grade and purified where necessary.

*4.2. 4-Hydroxybutenolide **2***

A solution of freshly distilled furfural (236 g, 2.46 mol) in 2300 mL 95% ethanol containing 2 g Rose bengal was irradiated using a 1000 W tungsten–iodine lamp in a Pyrex reactor, with the internal temperature maintained at 25–31°C, and oxygen was bubbled continuously through the reaction solution with effective stirring. Irradiation was continued for approximately 35 h, by which time the furfural had been consumed, as monitored by TLC. The solution was removed by rotary evaporation to yield (172 g) fresh yellow crude **2** (70%). This product was pure enough to be used in the next step. Recrystallization from benzene yielded white crystalline **2**, mp 54–55°C (lit.[8], mp 49–53°C).

4.3. Epimeric mixture of 5-[(1R,2S,5R)-menthyloxy]-2(5H)-furanone **3a**+**3b**

To a solution of **2** (20 g, 0.2 mol) and (1*R*,2*S*,5*R*)-(−)-menthol (31.3 g, 0.2 mol) in anhydrous benzene (200 mL) was added 2–3 drops of condensed sulfuric acid as a catalyst. The reaction mixture was refluxed for 8 h with continuous removal of water by azeotropic separation. The mixture was washed with 10% $NaHCO_3$ solution and brine, and then dried and evaporated. The resulting oil solidified immediately at room temperature. After removal of the menthol remaining in the crude product by washing with cold petroleum (30–60°C), the epimeric mixture **3a**+**3b** (44 g, 93%) was obtained as a pale yellow solid and used directly in the next step. Recrystallization of **3a**+**3b** from petroleum ether yielded enantiomerically pure **3a**. $[\alpha]_D^{22}$=−141.5; mp 76–77°C (lit.[4], mp 70.5–70.7°C).

4.4. 5-(R)-(l-Menthyloxy)-3-bromo-2(5H)-furanone **5a**

To a solution of **3a**+**3b** (48 g, 0.2 mol) in anhydrous benzene (200 mL) at room temperature was added dropwise bromine (32 g, 0.2 mol). The reaction mixture was stirred at room temperature for 12 h, by which time the epimeric mixture **3a**+**3b** had been consumed, as monitored by TLC. The stirring was continued at 0°C on an ice bath and pyridine (32 mL, 0.4 mol) was added 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 under vacuum. The epimeric mixture **5a**+**5b** (58 g, 91%) was obtained as a brown-yellow solid. The epimeric mixture **5a**+**5b** was checked by ^{1}H NMR analysis, **5a**:**5b**, 6:4; δ_{5a} (CCl_4)=5.97 (0.6H, s, H-5a); δ_{5b} (CCl_4)=5.87 (0.4H, s, H-5b). Enantiomerically pure **5a** (18.5 g) was obtained as pale yellow crystals in 29% yield after two crystallizations from petroleum ether (30–60°C). The ^{1}H NMR spectra showed a single epimer **5a**, δ_{5a} (CCl_4)=5.97 (0.6H, s, H-5a) and had lost the characteristic shift of **5b**. The mother liquors were evaporated and the residue crystallized 2–3 times from petroleum ether as described above to afford additional enantiomerically pure **5a** (combined yield 48%). Compound **5a**: as pale yellow crystals, mp 89–90°C (from petroleum ether); $[\alpha]_D^{20}$=−121.1 (*c* 1.82, $CHCl_3$); UV (λ_{max}, 95% Et0H), 251.0 (lg ε 3.6) nm; IR (KBr, cm^{-1}): 2910, 2850, 1761, 1612, 1152, 925; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80 (3H, d, *J*=7.2 Hz), 0.86 (3H, d, *J*=6.8 Hz), 0.95 (3H, d, *J*=6.8 Hz), 1.10 (2H, m), 1.42 (2H, m), 1.67 (2H, m), 2.10 (3H, m), 3.25 (1H, bt, *J*=10.8, 10.8, 4.6 Hz), 5.97 (1H, s), 7.20 (1H, s); ^{13}C NMR (45 MHz, $CDCl_3$): δ 15.6, 20.8, 22.1, 22.9, 25.3, 31.3, 34.0, 40.2, 47.6, 79.2, 99.7, 117.5, 147.5, 166.0; EIMS *m/z*: 316 (M^+, 18), 301, 288, 73 ($C_2HO_3^+$, 100); anal. calcd for $C_{14}H_{21}O_3Br$: C, 53.01; H, 6.67; found: C, 52.93; H, 6.85. The structure for **5a** was confirmed by X-ray crystallography (Fig. 1).

4.5. General procedure for the preparation of spiro-cyclopropane derivative **8a**–**8h**

The alcohol nucleophilic reagent (4–7 mmol) under an N_2 atmosphere was added to a mixture of powdered K_2CO_3 (1.11 g, 8 mmol), tetrabutylammonium bromide (0.32 g, 1 mmol) and acetonitrile (6 mL). The mixture was stirred for 20 min. Then chiral synthon **5a** (0.63 g, 2 mmol) was added and the mixture was stirred at room temperature for 1–12 days, by which time the chiral synthon **5a** had been 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 was purified by column chromatography to give **8a**–**8f**.

4.6. *Spiro[1-bromo-4-*l*-menthyloxy-5-oxo-6-oxa-bicyclo[3.1.0]hexane-2,3′-(4′-diphenylmethoxy-5′-*l*-menthyloxybutyrolactone)]* ***8a***

Purification by flash chromatography (petroleum ether:EtOAc, 98:2) gave **8a** (0.62 g, 84%) as a white solid: R_f 0.51 (10% EtOAc–petroleum ether, 30–60°C); mp 154–155°C (white plates, from petroleum ether, 30–60°C); $[\alpha]_D^{20}$=−127.1 (*c* 1.110, $CHCl_3$); UV (λ_{max}, $CHCl_3$): 288.6 (lg ε 1.795), 275.4 (lg ε 1.826), 258.4 (lg ε 2.543), 252.9 (lg ε 2.561) nm; IR (KBr, cm^{-1}): 3066, 1789, 1129, 921; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.66 (3H, d, *J*=7.2 Hz), 0.69 (3H, d, *J*=6.8 Hz), 0.74 (3H, d, *J*=6.8 Hz), 0.78 (3H, d, *J*=7.2 Hz), 0.82 (3H, d, *J*=6.8 Hz), 0.86 (3H, d, *J*=6.8 Hz), 1.02–1.34 (10H, m), 1.34–1.47 (2H, m,), 1.52–1.80 (4H, m), 1.87–2.11 (2H, m), 3.05 (1H, s), 3.19 (1H, ddd, *J*=10.2, 4.08 Hz), 3.29 (1H, ddd, *J*=10.2, 4.08 Hz), 4.86 (1H, s), 5.20 (1H, s), 5.33 (1H, s), 5.50 (1H, s),7.34 (10H, m); ^{13}C NMR (45 MHz, $CDCl_3$): δ 15.5, 15.6, 20.6, 20.8, 21.9, 22.0, 22.7, 23.1, 24.7, 25.4, 31.1, 31.2, 33.9, 34.0, 34.3, 38.3, 38.6, 38.7, 39.5, 47.1, 47.2, 76.5, 78.5, 82.3, 86.1, 97.0, 100.7, 126.4, 127.3, 128.1, 128.6, 129.0, 140.7, 167.8, 169.0; EIMS *m/z*: 736 (M^+, 6), 669, 664, 632, 261 ($C_{15}H_{17}O_4^+$, 100); anal. calcd for $C_{41}H_{53}O_7Br$: C, 66.75; H, 7.24; found: C, 67.02; H, 7.47. The structure of **8a** was confirmed by X-ray crystallography (Fig. 2).

4.7. *Spiro[1-bromo-4-*l*-menthyloxy-5-oxo-6-oxa-bicyclo[3.1.0]hexane-2,3′-(4′-benzyloxy-5′-*l*-menthyloxybutyrolactone)]* ***8b***

Purification by flash chromatography (petroleum ether:EtOAc, 98:2) gave **8b** (0.46 g, 70%) as a white solid: R_f 0.86 (15% EtOAc–petroleum ether, 30–60°C); mp 120–122°C (white plates, from petroleum ether, 30–60°C); $[\alpha]_D^{20}$=−138.8 (*c* 0.77, $CHCl_3$); UV (λ_{max}, $CHCl_3$): 264.0 (lg ε 1.555), 258.1 (lg ε 1.663), 252.3 (lg ε 1.387) nm; IR (KBr, cm^{-1}) 3068, 1790, 1131, 921; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.73 (3H, d, *J*=7.2 Hz), 0.75 (3H, d, *J*=6.8 Hz), 0.78 (3H, d, *J*=6.8 Hz), 0.86 (3H, d, *J*=7.2 Hz), 0.91 (3H, d, *J*=6.8 Hz), 0.96 (3H, d, *J*=6.8 Hz), 1.18–1.46 (6H, m), 1.51–1.98 (6H, m), 1.99–2.19 (6H, m), 3.03 (1H, s), 3.45 (2H, ddd, *J*=10.2, 4.10 Hz), 3.53 (1H, s), 4.56 (2H, dd, *J*=10.66 Hz), 5.57 (1H, s), 5.64 (1H, s), 7.34 (5H, m); ^{13}C NMR (45 MHz, $CDCl_3$): δ 15.6, 15.6, 20.7, 20.8, 22.1, 22.2, 22.8, 23.2, 24.8, 25.4, 31.3, 31.4, 34.3, 34.0, 34.1, 38.3, 38.5, 39.0, 39.8, 47.3, 47.3, 73.2, 76.6, 78.4, 81.6, 99.9, 100.0, 128.5, 128.8, 128.9, 136.0, 167.8, 168.7; EIMS *m/z*: 562, 430, 137, 94, 91, 83, 55, 43, 41 ($C_3H_5^+$, 100); anal. calcd for $C_{35}H_{49}O_7Br$: C, 63.53; H, 7.46; found: C, 63.55; H, 7.57.

4.8. *Spiro[1-bromo-4-*l*-menthyloxy-5-oxo-6-oxa-bicyclo[3.1.0]hexane-2,3′-(4′-α-methylbenzyloxy-5′-*l*-menthyloxybutyrolactone)]* ***8c***

Purification by flash chromatography (petroleum ether:EtOAc, 98:2) gave **8c** (0.67 g, 88%) as a pale yellow oil: R_f 0.50 (10% EtOAc–petroleum ether, 30–60°C); $[\alpha]_D^{20}$=−159.5 (*c* 0.70, $CHCl_3$); UV (λ_{max}, C_2H_5OH): 215.9 (lg ε 2.35) nm; IR (KBr, cm^{-1}): 3060, 1784, 1123, 933; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.64 (3H, d, *J*=7.2 Hz), 0.70 (3H, d, *J*=6.8 Hz), 0.74 (3H, d, *J*=6.8 Hz), 0.74–1.02 (27H, m), 1.19–1.79 (24H, m), 1.89–2.23 (12H, m), 2.06 (6H, s), 2.93 (1H, s), 3.08 (1H, s), 3.20 (2H, ddd, *J*=10.30, 10.30, 4.12 Hz), 3.58 (2H, ddd, *J*=10.3, 10.3, 4.1 Hz), 3.64 (1H, s), 3.69 (1H, s), 4.43 (2H, m), 4.97 (1H, s), 5.31 (1H, s), 5.72 (1H, s), 5.87 (1H, s), 7.23–7.44 (10H, m); ^{13}C NMR (45 MHz, $CDCl_3$): δ 15.2, 15.4, 15.6, 20.4, 20.5, 20.6, 20.7, 21.9, 22.00, 22.1, 22.2, 22.5, 22.6, 22.9, 23.1, 24.4, 24.5, 25.1, 30.8, 31.1, 33.8, 34.00, 34.0, 37.7, 38.1, 38.4, 38.6, 38.3, 38.6, 38.9, 39.3, 47.0, 47.2, 47.3, 75.9, 76.3, 78.1, 79.3, 79.6, 80.5, 96.6, 100.2, 101.0, 125.7, 126.2, 126.4, 127.5, 128.2, 128.4, 128.5, 128.6, 128.8, 140.5, 141.6,

167.2, 167.5, 168.5, 169.0; FABMS *m/z*: 674 (M^+, 3), 139, 105 ($PhCH^+CH_3$, 100), 83; anal. calcd for $C_{36}H_{51}O_7Br$: C, 63.99; H, 7.61; found: C, 64.48; H, 7.63.

*4.9. Spiro[1-bromo-4-*l*-menthyloxy-5-oxo-6-oxa-bicyclo[3.1.0]hexane-2,3′-(4′-menthyloxy-5′-*l*-menthyloxybutyrolactone)]* ***8d***

Purification by flash chromatography (petroleum ether:EtOAc, 98:2) gave **8d** (0.68 g, 48%) as a white solid: R_f 0.43 (6% EtOAc–petroleum ether, 30–60°C); mp 53–55°C (white crystals from petroleum ether, 30–60°C); $[\alpha]_D^{20}=-141.7$ (*c* 0.55, $CHCl_3$); UV (λ_{max}, $CHCl_3$): 243.2 (lg ε 1.399) nm; IR (KBr, cm^{-1}): 3067, 1787, 1122, 920; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.70 (3H, d, *J*=7.2 Hz), 0.75 (3H, d, *J*=6.8 Hz), 0.79 (3H, d, *J*=6.8 Hz), 0.83 (3H, d, *J*=7.2 Hz), 0.87 (3H, d, *J*=6.8 Hz), 0.93 (3H, d, *J*=6.8 Hz), 0.97 (3H, d, *J*=7.2 Hz), 1.02 (3H, d, *J*=6.8 Hz), 1.08 (3H, d, *J*=6.80 Hz), 1.17–1.50 (10H, m), 1.54–1.83 (9H, m), 1.89–2.33 (8H, m), 3.10 (1H, s), 3.24 (1H, bt, *J*=10.8, 10.8, 4.60 Hz), 3.56 (2H, bt, *J*=10.8, 10.8, 4.6 Hz), 3.65 (1H, s), 5.61 (1H, s), 5.73 (1H, s); ^{13}C NMR (45 MHz, $CDCl_3$): δ 15.2, 15.5, 15.6, 15.7, 20.8, 20.9, 21.3, 22.1, 22.2, 22.5, 22.7, 23.2, 24.7, 25.0, 25.4, 29.9, 31.3, 31.4, 33.8, 34.1, 34.1, 34.5, 38.4, 39.2, 39.3, 40.7, 42.7, 47.4, 48.2, 76.4, 78.8, 80.2, 80.6, 97.4, 103.2, 168.0, 169.1; EIMS *m/z*: 708 (M^+, 2), 562, 539, 247, 125, 97 ($C_4HO_3^+$, 100), 71, 43, 41; anal. calcd for $C_{38}H_{61}O_7Br$: C, 64.30; H, 8.66; found: C, 64.56; H, 9.12.

*4.10. Spiro[1-bromo-4-*l*-menthyloxy-5-oxo-6-oxa-bicyclo[3.1.0]hexane-2,3′-(4′-bornyloxy-5′-*l*-menthyloxybutyrolactone)]* ***8e***

Purification by flash chromatography (petroleum ether:EtOAc, 98:2) gave **8e** (0.45 g, 64%) as a white solid: R_f 0.69 (10% EtOAc–petroleum ether, 30–60°C); mp 59–60°C (white crystals, from petroleum ether, 30–60°C); $[\alpha]_D^{20}=-130.2$ (*c* 1.650, $CHCl_3$); UV (λ_{max}, $CHCl_3$): 284.8 (lg ε 2.070), 255.4 (lg ε 2.079), 242.0 (lg ε 0.413) nm; IR (KBr, cm^{-1}): 3074, 1793, 1127, 931; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.74 (3H, d, *J*=7.2 Hz), 0.75 (3H, d, *J*=6.8 Hz), 0.79 (3H, d, *J*=6.8 Hz), 0.88 (3H, d, *J*=7.2 Hz), 0.89 (3H, d, *J*=6.8 Hz), 0.91 (3H, d, *J*=6.8 Hz), 0.95 (3H, s), 0.97 (6H, s), 0.98–1.16 (4H, m), 1.20–1.49 (8H, m), 1.53–1.91 (6H, m), 1.95–2.36 (7H, m), 3.08 (1H, s), 3.49–3.74 (3H, m), 3.63 (1H, s), 5.67 (1H, s), 5.92 (1H, s); ^{13}C NMR (45 MHz, $CDCl_3$): δ 14.0, 15.9, 16.0, 19.0, 19.9, 20.1, 21.0, 21.1, 22.6, 23.1, 23.5, 25.1, 25.8, 26.7, 28.4, 31.6, 31.8, 34.4, 34.7, 38.1, 38.7, 39.3, 39.4, 40.5, 45.1, 47.7, 48.0, 50.0, 78.0, 78.9, 82.6, 86.5, 97.4, 100.6, 168.0, 169.5; EIMS *m/z*: 709 (M^++1, 12), 704, 692, 667, 652, 643, 617, 595, 96, 95 ($C_7H_{11}^+$, 100), 43; anal. calcd for $C_{38}H_{59}O_7Br$: C, 64.48; H, 8.40; found: C, 64.14, H, 8.32.

*4.11. Spiro[1-bromo-4-*l*-menthyloxy-5-oxo-6-oxa-bicyclo[3.1.0]hexane-2,3′-(4′-cycloheptyloxy-5′-*l*-menthyloxybutyrolactone)]* ***8f***

Purification by flash chromatography (petroleum ether:EtOAc, 98:2) gave **8f** (0.46 g, 68%) as a colorless oil: R_f 0.69 (10% EtOAc–petroleum ether, 30–60°C); $[\alpha]_D^{20}=-140.9$ (*c* 1.075, $CHCl_3$); UV (λ_{max}, $CHCl_3$): 261.0 (lg ε 1.727), 254.6 (lg ε 2.239), 248.8 (lg ε 2.039), 243.5 (lg ε 1.758) nm; IR (KBr, cm^{-1}): 3068, 1789, 1128, 922; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.73 (3H, d, *J*=7.2 Hz), 0.77 (3H, d, *J*=6.8 Hz), 0.80 (3H, d, *J*=6.8 Hz), 0.86 (3H, d, *J*=7.2 Hz), 0.92 (3H, d, *J*=6.8 Hz), 0.97 (3H, d, *J*=6.8 Hz), 1.17–1.47 (12H, m), 1.4.9–1.94 (12H, m), 1.96–2.25 (6H, m), 3.04 (1H, s), 3.45–3.63 (3H, m), 3.64 (1H, s), 5.55 (H, s), 5.82 (1H, s); ^{13}C NMR (45 MHz, $CDCl_3$): δ 15.4, 15.6, 20.5, 20.7, 22.0, 22.1, 22.3, 22.7, 23.0, 24.6, 25.3, 28.1, 28.5, 28.7, 31.1, 31.3, 32.8, 33.6, 33.9, 34.0, 34.7, 38.0, 38.3, 38.9,

39.7, 47.3, 76.3, 78.0, 78.6, 79.8, 96.5, 100.7, 167.5, 168.7; FABMS *m/z*: 666 (M^+, 15), 665, 636, 530 ($M^+-C_7H_{14}O_2$, 100), 494, 278; anal. calcd for $C_{35}H_{55}O_7Br$: C, 62.96; H, 8.30; found: C, 63.10; H, 8.56.

*4.12. Spiro[1-bromo-4-*l*-menthyloxy-5-oxo-6-oxa-bicyclo[3.1.0]hexane-2,3′-(4′-ethyloxylactate-5′-*l*-menthyloxybutyrolactone)]* ***8g***

Purification by flash chromatography (petroleum ether:EtOAc, 98:2) gave **8g** (0.33 g, 49%) as a white solid: R_f 0.44 (10% EtOAc–petroleum ether, 30–60°C); mp 102–103°C (white plates, from petroleum ether, 30–60°C); $[\alpha]_D^{20}=-146.94$ (*c* 0.905, $CHCl_3$); UV (λ_{max}, $CHCl_3$): 206.0 (lg ε 1.251) nm; IR (KBr, cm^{-1}) 3065, 1782, 1740, 1138, 926; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (3H, d, *J*=7.0 Hz), 0.81 (3H, d, *J*=6.9 Hz), 0.86 (3H, d, *J*=6.9 Hz), 0.88 (3H, d, *J*=7.0 Hz), 0.91 (3H, d, *J*=6.9 Hz), 0.94 (3H, d, *J*=6.9 Hz), 0.96–1.30 (4H, m), 1.32 (3H, t, *J*=7.0 Hz), 1.43 (3H, d, *J*=6.9 Hz), 1.45–1.65 (6H, m), 2.09–2.12 (6H, m), 3.08 (1H, s), 3.58–3.61 (2H, ddd, *J*=10.8, 4.20 Hz), 3.68 (1H, s), 4.20 (H, q, *J*=7.2 Hz), 4.25 (2H, q, *J*=7.2 Hz), 5.62 (1H, s), 6.19 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 16.5, 16.6, 19.2, 20.0, 21.7, 21.8, 23.1, 23.68, 24.1, 26.0, 26.4, 32.3, 32.4, 34.1, 34.5, 35.0, 35.1, 39.0, 40.0, 41.0, 48.3, 62.5, 74.6, 78.3, 79.5, 80.9, 97.8, 98.5, 168.7, 169.6, 172.0; FABMS *m/z*: 671 (M^++1, 52), 670 (M^+, 6), 533, 397, 139, 83 ($C_4H_3O_2^+$, 100); anal. calcd for $C_{33}H_{51}O_9Br$: C, 59.01; H, 7.65; found: C, 59.20; H, 7.94. The structure for **8g** was confirmed by X-ray crystallography (Fig. 3).

*4.13. Spiro[1-bromo-4-*l*-menthyloxy-5-oxo-6-oxa-bicyclo[3.1.0]hexane-2,3′-(4′-ethyloxyacetate-5′-*l*-menthyloxybutyrolactone)]* ***8h***

Purification by flash chromatography (petroleum ether:EtOAc, 98:2) gave **8h** (0.24 g, 37%) as a white solid: R_f 0.48 (10% EtOAc–petroleum ether, 30–60°C); mp 161–162°C (white crystals, from petroleum ether, 30–60°C); $[\alpha]_D^{20}=-150.2$ (*c* 0.6, $CHCl_3$); UV (λ_{max}, 95% C_2H_5OH): 204.9 (lg ε 0.393) nm; IR (KBr, cm^{-1}): 3070, 1795, 1745, 1138, 923; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (3H, d, *J*=7.2 Hz), 0.81 (3H, d, *J*=6.8 Hz), 0.85 (3H, d, *J*=6.8 Hz), 0.89 (3H, d, *J*=7.2 Hz), 0.91 (3H, d, *J*=6.8 Hz), 0.95 (3H, d, *J*=6.8 Hz), 1.05–1.14 (6H, m), 1.36–1.42 (4H, m), 1.36 (3H, t, *J*=7.2 Hz), 1.75–1.79 (4H, m), 2.20–2.23 (4H, m), 3.19 (1H, s), 3.58–3.61 (2H, ddd, *J*=10.5, 4.95 Hz), 3.77 (1H, s), 4.13 (2H, d, *J*=15.9 Hz), 4.33 (2H, q, *J*=7.2 Hz), 5.89 (1H, s), 6.20 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 15.5, 16.6, 20.7, 20.8, 21.0, 22.2, 22.8, 23.1, 24.7, 25.4, 31.3, 31.4, 34.1, 34.1, 34.5, 38.5, 38.7, 39.1, 40.0, 47.4, 61.5, 67.2, 77.4, 78.5, 82.4, 97.5, 99.7, 167.8, 168.4, 168.6; FABMS *m/z*: 656 (M^++1, 18), 545, 543, 139, 83 ($C_4H_3O_2^+$, 100); anal. calcd for $C_{32}H_{49}O_9Br$: C, 58.52; H, 7.52; found: C, 58.91; H, 7.75.

Acknowledgements

Financial support of this work by the National Natural Science Foundation of China is gratefully acknowledged.

References

1. Huang, H.; Chen, Q. *Tetrahedron: Asymmetry* **1998**, *9*, 4103.
2. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley: New York, 1995; p. 43.
3. (a) Van Oeveren, A.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem*. **1994**, *59*, 5999. (b) Pelter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. *Tetrahedron: Asymmetry* **1992**, *3*, 239.

4. (a) Feringa, B. L.; de Lange, B.; Jong, C. *J. Org. Chem*. **1989**, *54*, 2471. (b) Feringa, B. L.; de Jons, J. C. *Bull. Soc. Chim. Belg*. **1992**, *101*, 627. (c) de Jons, J. C.; Bolhuis, F. V.; Feringa, B. L. *Tetrahedron: Asymmetry* **1991**, *2*, 1247.
5. (a) Farina, F.; Maestro, M. C.; Martin, M. R.; Martin, M. V.; Sanchez, F.; Soria, M. L. *Tetrahedron* **1986**, *42*, 3715. (b) Farina, F.; Maestro, M. C.; Martin, M. R.; Martin, M. V.; Sanchez, F. *J. Chem. Res. (S)* **1984**, *44*. (c) Farina, F.; Maestro, M. C.; Martin, M. R.; Martin, M. V.; Sanchez, F. *Heterocycles* **1983**, *20*, 1761. (d) Farina, F.; Martin, M. R.; Martin, M. V. *Anales de Quimica* **1978**, *74*, 799. (e) Farina, F.; Martin, M. R.; Martin, M. V. *Anales de Quimica* **1979**, *75*, 144.
6. (a) Chen, Q.; Zou, C. *Youji Huaxue* (*Organic Chemistry*, in Chinese) **1994**, *14*, 1. (b) Chen, Q.; Huang, B. *Chinese Science Bulletin* (in Chinese) **1994**, *39*, 2154. (c) Chen, Q.; Geng, Z. *Acta Chimica Sinica* (in Chinese) **1993**, *51*, 622. (d) Chen, Q.; Geng, Z.; Huang, B. *Tetrahedron: Asymmetry* **1995**, *6*, 401. (e) Cui, J.; Du, B.; Chen, Q. *Science in China* (series B) **1998**, *41*, 65. (g) Wang, Y.-H.; Chen, Q. *Science in China* (series B, in Chinese) **1998**, *28*, 531.
7. Gollnic, K.; Geiesbeck, A. *Tetrahedron* **1985**, *53*, 2057.
8. (a) Gen, Z. M. S. Thesis, Beijing Normal University, 1991, (b) Haung, B. M. S. Thesis, Beijing Normal University, 1992.
9. The atomic coordinates for the X-ray structures have been deposited with the Cambridge Crystallographic Data Centre.