Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 4103–4107

TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiomerically pure spiro-cyclopropane derivatives containing multichiral centers

Hui Huang † and Qinghua Chen *

Department of Chemistry, Beijing Normal University, Beijing 100875, P.R. China

Received 10 September 1998; accepted 7 October 1998

Abstract

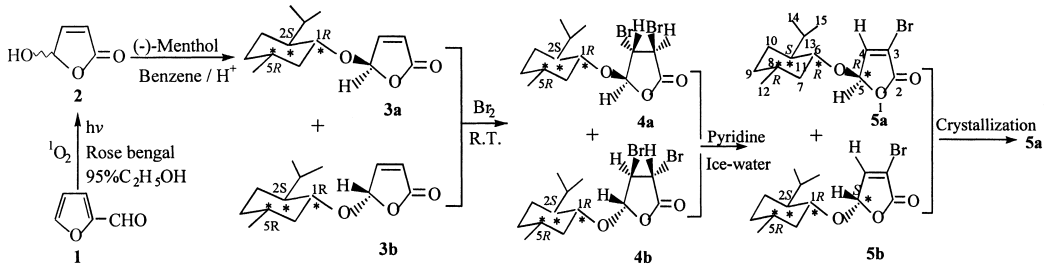
A novel chiral source, 5-(*R*)-[(1*R*,2*S*,5*R*)-(−)-menthyloxy]-3-bromo-2(5H)-furanone (**5a**), was obtained in 46% yield with d.e.≥98% from the epimeric mixture of 5-(*l*-menthyloxy)-3-bromo-2(5H)-furanone (**5a**+**5b**) obtained via the bromination of an epimeric mixture of 5-(*l*-menthyloxy)-2(5H)-furanone (**3a**+**3b**) followed by the elimination of hydrogen bromide. The asymmetric reaction of **5a** with a nucleophilic alcohol afforded enantiomerically pure spiro-cyclopropane derivatives containing four stereogenic centers, **9a**–**9e**, in 50–68% yield with d.e.≥98%. The enantiomerically pure compounds **9a**–**9e** were identified on the basis of their analytical data and spectroscopic data, such as $[\alpha]_D^{20}$, UV, IR, ^{1}H NMR, ^{13}C NMR, MS and elementary analysis. The absolute configuration of the chiral spiro-cyclopropane compound **9a** was established by X-ray crystallography.

Recently, chiral sources obtained from natural chiral auxiliaries, such as (1*R*,2*S*,5*R*)-(−)-menthol and endo-(−)-borneol, have attracted much attention in the asymmetric synthesis of some biologically active compounds.[1–4] It has been known that the chiral reagent 5-(*l*-menthyloxy)-2(5H)-furanone behaves as a Michael acceptor towards carbon, oxygen, sulfur and nitrogen nucleophiles to give chiral 5-(*l*-menthyloxy)-4-substituted-butyrolactones.[2–4] The 5-(*l*-menthyloxy)-3,4-dihalo(chloro or bromo)-2(5H)-furanone reacts readily with nitrogen and sulfur nucleophiles to give the tandem Michael addition/elimination products, 5-(*l*-menthyloxy)-4-substituted-3-halo-2-(5H)-furanones.[4] We have now successfully synthesized the novel chiral source, 5-(*R*)-[(1*R*,2*S*,5*R*)-(−)-menthyloxy)]-3-bromo-2(5H)-furanone (**5a**), which was obtained in 46% yield with d.e.≥98% (Scheme 1) from the epimeric mixture of 5-(*l*-menthyloxy)-3-bromo-2(5H)-furanone (**5a**+**5b**) via the bromination of an epimeric mixture of 5-(*l*-menthyloxy)-2(5H)-furanone (**3a**+**3b**) followed by the elimination of hydrogen bromide.[5] After recrystallization of the epimeric mixture, the ^{1}H NMR spectrum showed a single epimer **5a**: δ_{5a}=5.97 (1H, s, C_5–H_{5a}) ppm, and lost the characteristic shift of **5b**: δ_{5b}=5.87 (1H, s, C_5–H_{5b}) ppm. Enantiomerically

* Corresponding author. Fax: (+) 010-62200567; e-mail: qinghuac@bnu.edu.cn

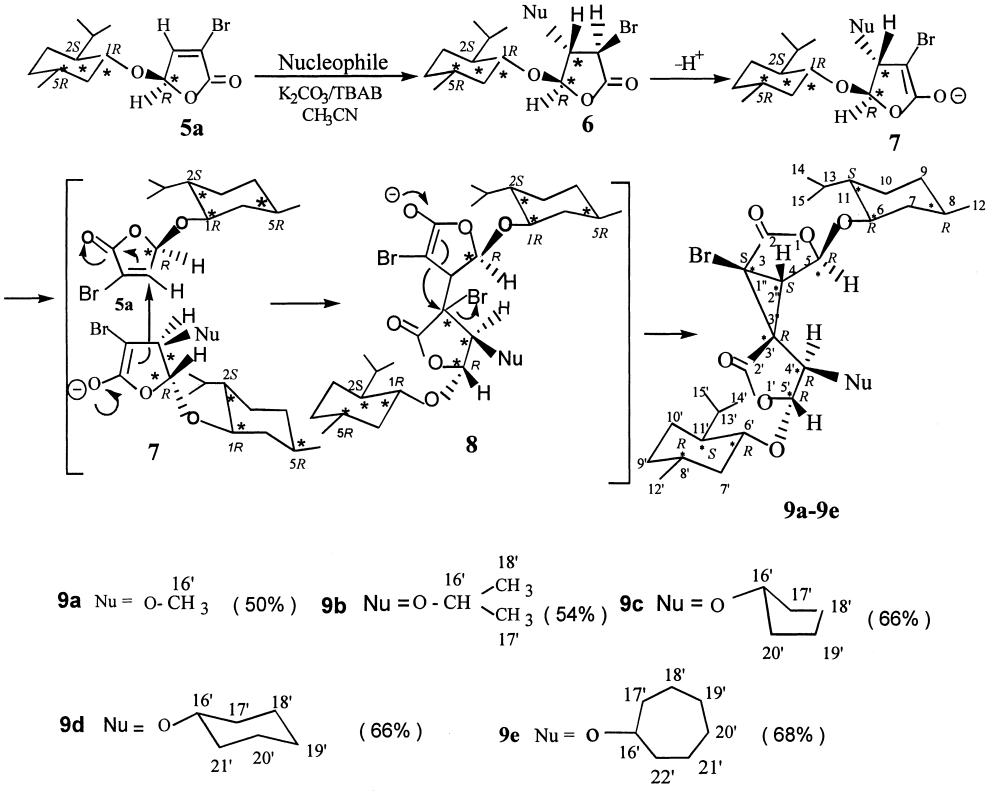
† Visiting Scholar, Associate Professor, Department of Chemistry, Tonghua Teacher's College, Tonghua, 134002, Jilin, P.R. China.

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00416-9



Scheme 1. The synthetic route to the chiral source **5a**

pure **5a** was obtained as pale-yellow needles, m.p. 89–90°C (petroleum ether, 30–60°C). The novel chiral source, 3-bromo-2(5H)-furanone **5a** was identified on the basis of its satisfactory elemental analysis data and spectroscopic data (IR, UV, ^{1}H NMR, ^{13}C NMR and MS).[5] The absolute configuration at the acetal of **5a** was shown to be *R* by means of an X-ray structure analysis of its asymmetric reaction product with methanol.[6] On the basis of previous work,[7] we have accomplished the tandem asymmetric double Michael addition/internal nucleophilic substitution of 5-(*R*)-(*l*-menthyloxy)-3-bromo-2(5H)-furanone (**5a**) with oxygen nucleophiles such as methanol, isopropanol, cyclopentanol, cyclohexanol 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, spirocyclopropane bisbutyrolactones **9a**–**9e** with four stereogenic centers were obtained in 50–68% yield



Scheme 2. The synthetic route to **9a**–**9e**

with d.e.≥98% by the tandem asymmetric reaction under the mild conditions indicated in Scheme 2. The spiro-cyclopropane bisbutyrolactones **9a**–**9e** were identified on the basis of their analytical data and spectroscopic data.[8] The absolute configuration of the chiral spiro-cyclopropane bisbutyrolactone **9a** was established by X-ray crystallography[6] and by spectroscopic analysis. The presence of two 5-menthyloxy-2(5H)-furanone moieties was deduced from the ^{1}H NMR spectrum, which showed two signals at δ: 5.64 (1H, s, H-5′), 5.66 (1H, s, H-5) assignable to the acetal protons. In addition, the ^{1}H NMR spectrum showed two signals at δ: 2.98 (1H, s, H-4), 3.42 (1H, s, H-4′), in which the absence of coupling constants between the vicinal protons H-4/H-5 and H-4′/H-5′ established a *trans* relationship. The presence of an IR band at 3078 cm^{-1} was assignable to a C–H stretching in a cyclopropane ring and the signal at δ 38.47 (C-4) ppm of the ^{13}C NMR spectrum was also in agreement with the presence of a cyclopropane ring. On the basis of these data, the proposed structure of spiro-cyclopropane bisbutyrolactone **9a** was consistent with the stereochemistry of the molecule of **9a** by its X-ray structure analysis. The ORTEP drawing and the crystal packing of the molecule of **9a** are shown in Figs. 1 and 2, respectively. The absolute configuration of (1*R*,2*S*,5*R*)-(−)-menthyloxy was unchanged during the asymmetric reaction process. Accordingly, the absolute configuration of **9a** was established and the configuration of the new stereogenic centers established as 3(*S*), 4(*S*), 3′(*R*), 4′(*R*).

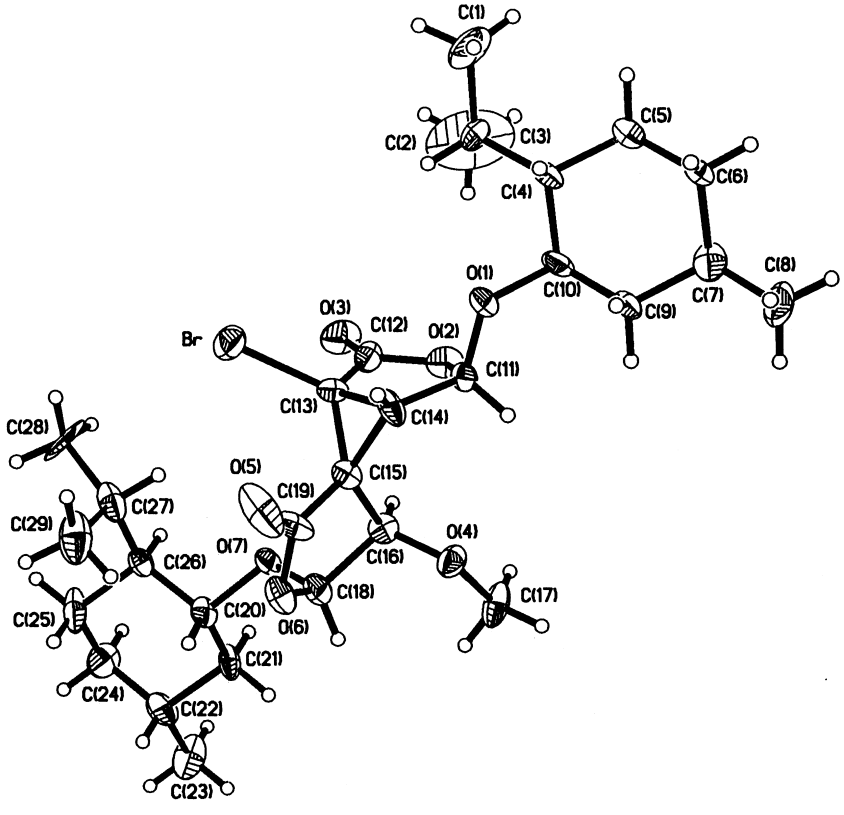


Figure 1. The ORTEP drawing of the molecule of **9a**

The behavior of 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,[7] such that the chiral 3-bromo furanone **5a** reacts readily with nucleophiles to give the Michael adduct **6**. When an anion, such as a carbanion, is used as a nucleophile, the carbanionic intermediate of type **7**, in the absence of

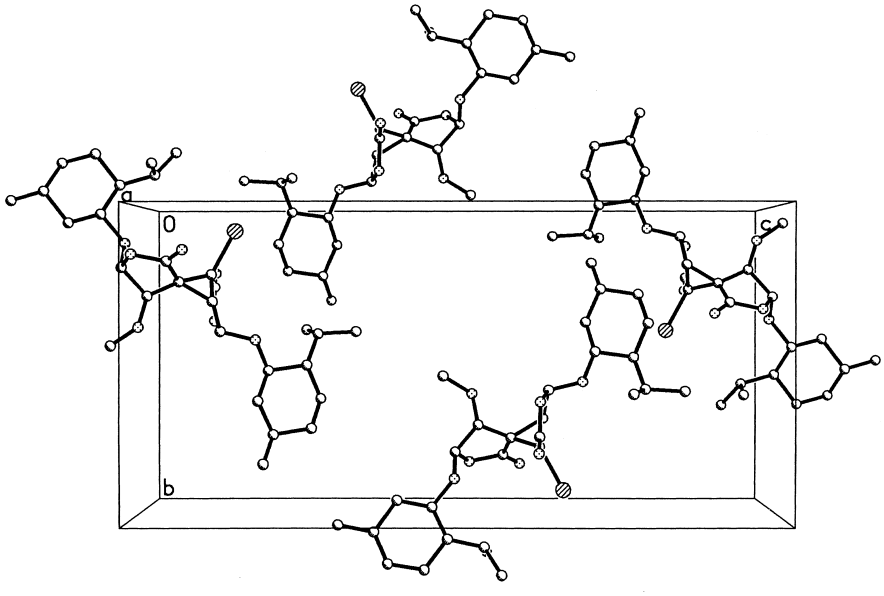


Figure 2. The crystal packing of the molecule of **9a**

a proton donor, adds to a second molecule of bromofuranone **5a** to give a new anionic intermediate, the enolate anion **8**. This intermediate, at room temperature, suffers an internal nucleophilic substitution of the halogen to yield the optically active spiro-cyclopropane bisbutyrolactones **9a**–**9e**. At present, we have also studied the asymmetric reaction of chiral 3-halo-2(5H)-furanone with different series of nucleophilic reagents such as carbon, oxygen, nitrogen and sulfur nucleophiles. Application of this synthetic strategy to the new optically active spiro-cyclopropane derivatives in asymmetric synthesis is currently under investigation.

Acknowledgements

We are grateful to the National Natural Science Foundation of China for supporting this research work.

References

1. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley: New York, 1995; p. 43.
2. (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.
3. (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*(7), 627.
4. (a) Chen, Q.; Geng, Z.; Huang, B.; Cao, P. *Youji Huaxue* (*Organic Chemistry*, in Chinese) **1991**, *11*, 494; (b) Chen, Q.; Zou, C. *Youji Huaxue* (*Organic Chemistry*, in Chinese) **1994**, *14*, 1; (c) Chen, Q.; Huang, B. *Chinese Science Bulletin* (in Chinese) **1994**, *39*, 2154; (d) Chen, Q.; Geng, Z. *Acta Chimica Sinica* (in Chinese) **1993**, *51*, 622; (e) Chen, Q.; Geng, Z.; Huang, B. *Tetrahedron: Asymmetry* **1995**, *6*, 401; (f) Cui, J.; Du, B.; Chen, Q. *Science in China (series B)* **1998**, *41*, 65.
5. **5a**: 0.73 g, (46%), m.p. 89–90°C; $[\alpha]_D^{20}=-121.1$ (*c* 1.82, $CHCl_3$); $C_{14}H_{21}O_3Br$, calcd: C, 53.01; H, 6.67; found: C, 52.93; H, 6.85); UV λ_{max} (95% EtOH): 251.0 (log ε 3.6) nm; IR (KBr, cm^{-1}): 2910, 2850 (CH), 1761 (C=O), 1612 (C=C), 1152 (COC, V_{as}), 925 (COC, V_s); ^1H NMR (200 MHz, $CDCl_3$) δ_H: 0.80 (3H, d, *J*=7.2 Hz, 3H-12), 0.86 (3H, d, *J*=6.8 Hz, 3H-14), 0.95 (3H, d, *J*=6.8 Hz, 3H-15), 1.10 (2H, m, 2H-10), 1.40 (2H, m, 2H-9), 1.67 (2H, m, 2H-7), 2.10 (3H, m, H-8, H-11, H-13), 3.25 (1H, bt, *J*=10.8, 10.8, 4.6 Hz, H-6), 5.90 (1H, S, H-5), 7.20 (1H, s, H-4) ppm; ^{13}C NMR (45 MHz,

$CDCl_3$) δ_C: 15.58 (C-15), 20.78 (C-14), 22.09 (C-12), 25.31 (C-13), 22.94 (C-10), 31.34 (C-8), 34.01 (C-9), 40.16 (C-7), 47.57 (C-11), 79.24 (C-6), 99.69 (C-5), 117.51 (C-4), 147.49 (C-3), 165.98 (C-2); m/z: 316 (M^+, 18), 301 (M^+-CH_3, 18), 288 ($M^+-C_2H_4$, 16), 73 ($C_2HO_3^{+\cdot}$, 100).

6. The stereochemistry of **9a** has been determined by a single crystal X-ray analysis. Crystal data: $C_{29}H_{45}O_7Br$, *Mr*=585.56, orthorhombic system, $P2_12_12_1$ space group, *a*=9.748(4) Å, *b*=12.537(5) Å, *c*=25.851(9) Å, *V*=3.159 $Å^3$, *Z*=4, *D*x=1.231 g cm^{-3}, μ=13.41 cm^{-1}, *F*(000)=1240. Monochromated Mo-K_α diffraction, λ=0.71073 Å, *R*=0.0475, R_w=0.0609, 3830 independent points, 865 perceivable points of $I \geq 3\sigma(I)$.
7. Farina, F.; Maestro, M. C.; Martin, M. R.; Martin, M. V.; Sanchez, F.; Soria, M. L. *Tetrahedron* **1986**, *42*(13), 3715.
8. 5-(*R*)-(*l*-Menthyloxy)-3-bromo-butyrolacto-[3,4,1′′,2′′]-spiro[4.2]-[cyclopropane-3′′,3′]-4′-methoxy-5′-(*R*)-(*l*-menthyloxy)-butyrolactone **9a**: 0.29 g (50%); white crystals, m.p. 156–158°C (petroleum ether, 30–60°C); $[\alpha]_D^{20}=-108.4$ (*c* 1.02, $CHCl_3$); $C_{29}H_{45}O_7Br$, calcd: C, 59.58; H, 7.75; found: C, 59.72; H, 8.07; UV: (λ_{max}, $CHCl_3$): 241.8 (log ε 0.70) nm; IR (KBr, cm^{-1}): 3077.8 (cyclopropane C–H), 1789.7 (C=O), 1123.4 (COC, Vas), 920.6 (COC, Vs); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H: 0.66 (3H, d, *J*=7.2 Hz, 3H-12′), 0.70 (3H, d, *J*=6.8 Hz, 3H-14′), 0.72 (3H, d, *J*=6.8 Hz, 3H-15′), 0.79 (3H, d, *J*=7.2 Hz, 3H-12), 0.84 (3H, d, *J*=6.8 Hz, 3H-14), 0.89 (3H, d, *J*=6.8 Hz, 3H-15), 1.09–1.45 (6H, m, 2H-10, 2H-10′, H-9e, H-9e′), 1.49–1.69 (6H, m, 2H-7, 2H-7′, H-9a, H-9a′), 1.89–2.17 (6H, m, H-8, H-8′, H-11, H-11′, H-13, H-13′), 2.98 (1H, s, H-4), 3.28 (3H, s, H-16′), 3.42 (1H, s, H-4′), 3.59 (2H, m, H-6, H-6′), 5.64 (1H, s, H-5′), 5.66 (1H, s, H-5) ppm; ^{13}C NMR (45 MHz, $CDCl_3$) δ_C: 15.57 (C-15′), 15.61 (C-15), 20.72 (C-14′), 20.81 (C-14), 22.09 (C-12′), 22.19 (C-12), 22.81 (C-10′), 23.11 (C-10), 24.79 (C-13′), 25.40 (C-13), 31.27 (C-8′), 31.32 (C-8), 34.05 (C-3′), 34.07 (C-9′), 34.15 (C-9), 38.47 (C-4), 38.50 (C-3), 39.11 (C-7′), 40.02 (C-7), 47.34 (C-11′), 47.43 (C-11), 57.42 (C-16′), 76.78 (C-6), 78.38 (C-6′), 82.48 (C-4′), 97.23 (C-5′), 99.26 (C-5), 167.76 (C-2′), 168.74 (C-2); m/z: 584 (M^+, 15), 540 [$(M-C_3H_8)^+$, 15] 454 [$(M-C_{10}H_{10})^+$, 15] 83 ($C_4H_3O_2^+$, 100), 43 ($C_3H_7^+$, 96), 41 ($C_3H_5^+$, 53).