DOI: 10.1002/cjoc.201200904

Towards Stereochemical Control: Two Approaches for the Highly *anti*-Diastereoselective Construction of the Spirolactone Moieties of Some *Stemona* Alkaloids†

Shichuan Tuo, Xuekui Liu, and Peiqiang Huang*

Department of Chemistry and Fujian Provincial Key Laboratory for Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, China

Some *Stemona* alkaloids belonging to the tuberostemospironine group possess a spirolactone moiety with *anti*-configuration (C-9/C-9a). In this paper, we describe two approaches to this structural unity. By using bromine atom as a traceless directing group, the SmI_2-mediated reductive coupling of ketone **6** and *β*-bromomethacrylate proceeded with complete *anti*-diastereoselectivity. In the absence of an *α*-directing (chelation) group, the one-pot reaction of the ketone derived from alcohol **15** with the organozinc reagent generated from bromomethacrylate afforded spiro-*α*-methylene-*γ*-lactone derivative **16** as a single diastereomer. These two highly diastereoselective methods would find application in the synthesis of stemona alkaloids containing *anti*-configured spiro-lactone/pyrrolidine moieties. In addition, on the basis of our previous work, the total synthesis of (–)-9-*epi*-11-demethylsessilifoliamide J (**11**), and an improved synthesis of (–)-9,11-di-*epi*-sessilifoliamide J (**9**) were accomplished.

Keywords *Stemona* alkaloids, spirolactone, SmI_2, organozinc reagent, sessilifoliamide J

Introduction

Selective synthesis is one of the major pursuits in organic synthesis.[1] Although a huge number of selective methods available,[2] the absolute control of diastereoselectivity is still challenging for organic chemists.

γ-Butyrolactone is a motif found in many bioactive natural products and pharmaceuticals.[3] In particular, *α*-methyl-*γ*-butyrolactone moiety, either fused, spiral, and/or appended to the core, is found in many *Stemona* alkaloids[4] such as the tuberostemospironine group (Figure 1). For the appended lactone/pyrrolidine moiety, the *anti*-stereochemistry is characteristic, as can be seen from Figure 1, however, both *syn* [*e.g.* sessilifoliamide J[5] (**1**) and croomine (**2**)] and *anti* [*e.g.* tuberspironine (**3**) and dehydrocroomine (**4**)] stereochemistries are found in the spirolactone/pyrrolidine moieties.

As a part of a general program aimed at the total synthesis of alkaloids,[6] we have recently disclosed the total synthesis of 9-*epi*-sessilifoliamide J (**8**)[7,8] and sessilifoliamide J (**1**).[9] In those syntheses, the SmI_2-mediated[10] reductive coupling-lactonization method[11] has been used for the first time for the construction of the spirolactone moiety. Although a good yield (70%) was obtained over two steps, the diastereoselectivities were poor (C-9/C-9a *syn*/*anti*＝27∶73, 11(*S*)/(*R*)＝41∶59)[8] (Scheme 1).

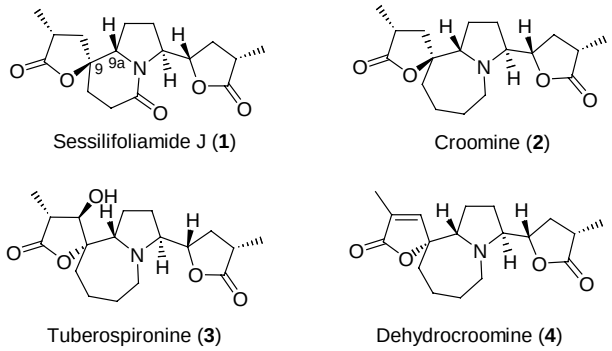
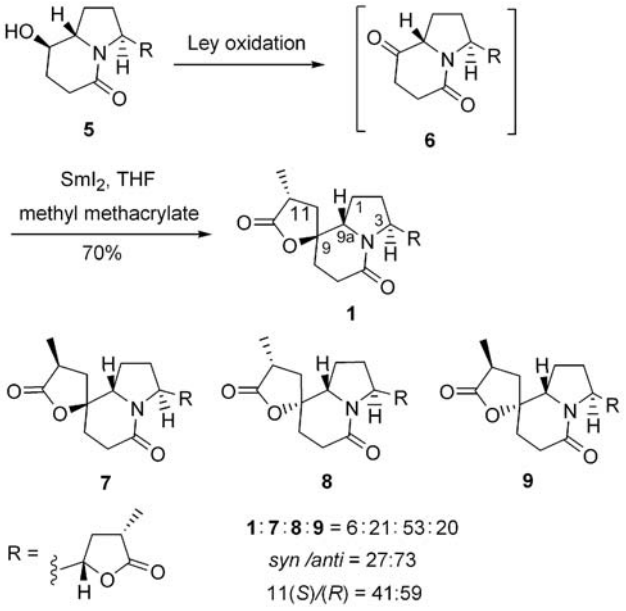


Figure 1 The structures of some *Stemona* alkaloids of tuberostemospironine group.

In view of the presence of the spirolactone/pyrrolidine moiety in either *syn* or *anti* form in many *Stemona* alkaloids, we undertook further investigations into developing highly diastereoselective methods for the construction of the spirolactone ring system. And the results are reported herein.

* E-mail: pqhuang@xmu.edu.cn
Received September 13, 2012; accepted October 31, 2012; published online December 11, 2012.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201200904 or from the author.
† Dedicated to the Memory of Professor Weishan Zhou.

Scheme 1 Synthesis of (−)-9-*epi* and (−)-sessilifoliamide J



Experimental

General methods

Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts (δ) are expressed in ppm units downfield from TMS. Silica gel (300−400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/hexane. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2. SmI_2 was freshly prepared from Sm and I_2 as a 0.1 mol•L^{-1} solution in THF. High-resolution mass spectra were obtained using electrospray ionization (ESI). NMO＝*N*-methylmorpholine-*N*-oxide; TPAP ＝ tetrapropylammonium perruthenate.

(2*S*,3'*S*,8a'*R*/*S*)-3'-[(2*S*,4*S*)-4-Methyl-5-oxotetrahydrofran-2-yl]tetrahydro-1'*H*,3*H*-spiro[furan-2,8'-indolizine]-5,5'(4*H*,8a'*H*)-dione (–)-11-demethylsessilifoliamide J (10) and (–)-9-*epi*-11-demethylsessilifoliamide J (11)

To a solution of alcohol **5** (20 mg, 0.079 mmol) in CH_2Cl_2 (2 mL) were added 4 Å molecular sieves (33 mg), NMO (14 mg, 0.12 mmol) and TPAP (2 mg, 0.006 mmol). The resultant mixture was stirred at room temperature for 50 min. The mixture was concentrated under reduced pressure and the residue was filtered through an Al_2O_3 pad eluting with ether. The solvent was removed under reduced pressure to afford the crude ketone, which was used in the next step without further purification. To a cooled solution (0 ℃) of the above mentioned crude ketone in THF (1 mL) were added successively methyl acrylate (119 mg, 0.67 mmol), *t*-BuOH (0.037 mL, 0.40 mmol), and 0.1 mol/L solution of SmI_2 in THF (2.4 mL, 0.24 mmol). After being stirred at the same temperature for 30 min, water (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (4∶1) to afford lactones **10** and **11** (18 mg, 75%) as an inseparable diastereomeric mixture in a ratio of 75∶25 as determined by ^{1}H NMR. The mixture was separated by preparative HPLC under the following conditions: mobile phase: 10% CH_3CN/H_2O; flow rate ＝4 mL/min; UV detection, 210 nm; retention time: $t_{r(major)}$＝51 min, $t_{r(minor)}$＝60 min. Minor diastereomer **10**: white solid. m.p. 128−130 ℃ (MeOH); $[\alpha]_D^{20}$ −88 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.27 (d, *J*＝7.1 Hz, 3H), 1.68−1.76 (m, 1H), 1.80−1.97 (m, 2H), 2.20−2.22 (m, 6H), 2.37 (ddd, *J*＝18.0, 8.7, 5.6 Hz, 1H), 2.43 (ddd, *J*＝18.0, 8.7, 6.4 Hz, 1H), 2.49−2.74 (m, 4H), 3.87 (dd, *J*＝9.7, 6.3 Hz, 1H), 4.63 (ddd, *J*＝8.6, 6.1, 3.4 Hz, 1H), 4.72 (ddd, *J*＝10.7, 5.5, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8 (CH_3), 24.7 (CH_2), 26.8 (CH_2), 27.1 (CH_2), 28.3 (CH_2), 28.8 (CH_2), 31.2 (CH_2), 32.9 (CH_2), 35.6 (CH), 57.7 (CH), 65.2 (CH), 79.5 (CH), 83.5 (C), 168.7 (CO), 174.9 (CO), 178.7 (CO); MS (ESI) *m*/*z*: 330 (M＋Na$^+$, 100%); IR (film) ν_{max}: 2949, 1770, 1638, 1451, 1404, 1385, 1194, 1011 cm^{-1}. HRMS (ESI) calcd for [$C_{16}H_{21}NO_5$＋Na$^+$]: 330.1312; found 330.1312.

Major diastereomer **11**: white solid. m.p. 142−144 ℃ (MeOH); $[\alpha]_D^{20}$ −40 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (d, *J*＝7.1 Hz, 3H), 1.77−1.94 (m, 3H), 1.97−2.20 (m, 6H), 2.40 (ddd, *J*＝13.0, 8.5, 5.5 Hz, 1H), 2.49−2.74 (m, 4H), 2.50 (ddd, *J*＝18.2, 6.9, 1.8 Hz, 1H), 3.77 (dd, *J*＝8.6, 7.0 Hz, 1H), 4.62 (ddd, *J*＝10.7, 5.6, 2.6 Hz, 1H), 4.67 (ddd, *J*＝8.5, 4.6, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8 (CH_3), 25.0 (CH_2), 25.2 (CH_2), 27.9 (CH_2), 28.0 (CH_2), 30.0 (CH_2), 32.3 (CH_2), 33.4 (CH_2), 35.8 (CH), 57.5 (CH), 65.6 (CH), 81.3 (CH), 81.8 (C), 168.8 (CO), 175.4 (CO), 179.2 (CO); MS (ESI) *m*/*z*: 308 (M＋H$^+$, 100%); IR (film) ν_{max}: 2923, 1765, 1640, 1453, 1405, 1372, 1195 cm^{-1}. HRMS (ESI) calcd for [$C_{16}H_{21}NO_5$ ＋ H$^+$]: 308.1498; found 308.1497.

Methyl (*E*)-3-{(3*S*,8*R*,8a*S*)-8-hydroxy-3-[(2*S*,4*S*)-4-methyl-5-oxotetrahydrofuran-2-yl]-5-oxooctahydroindolizin-8-yl}-2-methylacrylate (12)

To a solution of alcohol **5** (17 mg, 0.067 mmol) in CH_2Cl_2 (2 mL) were added 4 Å molecular sieves (35 mg), NMO (12 mg, 0.10 mmol) and TPAP (2 mg, 0.006 mmol). The resultant mixture was stirred at room temperature for 50 min. The mixture was concentrated under reduced pressure and the residue was filtered through an Al_2O_3 pad eluting with ether. The solvent was removed under reduced pressure to afford the crude ketone, which was used in the next step without further

CHINESE JOURNAL OF CHEMISTRY

purification. To a cooled solution (0 ℃) of the above mentioned crude ketone in THF (1 mL) were added successively methyl (*E*)-3-bromo-2-methacrylate (119 mg, 0.67 mmol) and a 0.1 mol•L^{-1} solution of SmI_2 in THF (2.7 mL, 0.27 mmol). After being stirred at the same temperature for 30 min, the mixture was allowed to warm to room temperature and stirred for 30 min. The reaction was quenched by addition of water (2 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (4∶1) to afford compound **12** (14 mg, 60%) as a colorless oil. $[\alpha]_D^{20}$ –200 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (d, *J*=7.0 Hz, 3H), 1.70−1.92 (m, 3H), 1.77 (br s, 1H), 1.96−2.17 (m, 4H), 2.14 (d, *J*=1.6 Hz, 3H), 2.37 (ddd, *J*=12.9, 8.6, 5.6 Hz, 1H), 2.47 (ddd, *J*=18.3, 7.2, 1.5 Hz, 1H), 2.58 (ddd, *J*=18.3, 11.4, 7.2 Hz, 1H), 2.61−2.68 (m, 1H), 3.71 (dd, *J*=7.7, 7.7 Hz, 1H), 3.76 (s, 3H), 4.66 (ddd, *J*=8.7, 5.0, 3.3 Hz, 1H), 4.74 (ddd, *J*=10.6, 5.6, 3.3 Hz, 1H), 6.64 (q, *J*=1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.5 (CH_3), 14.9 (CH_3), 24.9 (CH_2), 25.7 (CH_2), 27.4 (CH_2), 32.5 (CH_2), 32.9 (CH_2), 35.6 (CH), 52.2 (CH_3), 57.9 (CH), 66.5 (CH), 71.5 (C), 80.3 (CH), 131.6 (C), 141.1 (CH), 168.5 (CO), 169.5 (CO), 179.2 (CO); MS (ESI) *m*/*z*: 374 (M+Na$^+$, 100%); IR (film) ν_{max}: 3384, 2986, 2910, 1760, 1712, 1617, 1407, 1384, 1260, 1113, 1022 cm^{-1}. HRMS (ESI) calcd for [$C_{18}H_{25}NO_6$+Na$^+$]: 374.1580; found 374.1569.

(–)-9-*epi*-Sessilifoliamide J (8) and (–)-9,11-di-*epi*-sessilifoliamide J (9)

To a suspension of 10% Pd/C (6 mg) in EtOAc (1 mL) was added a solution of compound **12** (6 mg, 0.017 mmol) in EtOAc (0.5 mL). The mixture was stirred under an atmosphere of H_2 for 10 h at room temperature. The solid was filtered through a Celite pad and washed with methanol, and the filtrate was concentrated under reduced pressure. To the residue were added THF (1 mL) and 3 mol•L^{-1} HCl (0.5 mL). The solution was stirred overnight and extracted with EtOAc (2 mL×3). The combined organic layers were washed with brine (1 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (4∶1) to afford a mixture of two diastereomers **8** and **9** (5 mg, 91%, *dr*=52∶48) as a white solid that was separated by preparative HPLC under the following conditions: mobile phase: 12% CH_3CN/H_2O; flow rate =4 mL/min; UV detection, 210 nm; retention time: t_{rA6} =30 min, t_{rA2}=39 min. The physical and spectroscopic data of **8** and **9** are identical with those we reported previously.[7]

Methyl (*E*)-3-[(2*S*,3*R*)-2-ethyl-3-hydroxy-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl]-2-methylacrylate (14)

To a solution of alcohol **13** (490 mg, 1.86 mmol) in CH_2Cl_2 (11 mL) was added 4 Å molecular sieves (930 mg), NMO (327 mg, 2.79 mmol) and TPAP (32 mg, 0.093 mol). After being stirred at room temperature for 50 min, the mixture was concentrated under reduced pressure. The residue was filtered through an Al_2O_3 pad eluting with ether and the solvent was removed under reduced pressure to afford the crude ketone, which was used in the next step without further purification. To a cooled solution (0 ℃) of the above crude ketone in THF (4 mL) were added successively methyl (*E*)-3-bromo-2-methacrylate (3311 mg, 18.6 mmol) and a 0.1 mol•L^{-1} solution of SmI_2 in THF (74.5 mL, 7.45 mmol). After being stirred at the same temperature for 30 min, the mixture was allowed to warm to room temperature and stirred for 30 min, then quenched with water. The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (2∶1) to afford compound **14** as a colorless oil (527 mg, 78%). $[\alpha]_D^{20}$ –113 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (t, *J*=7.6 Hz, 3H), 1.62−1.67 (m, 1H), 1.83 (d, *J*=1.5, 3H), 1.85 (s, 1H, OH, D_2O exchangeable), 1.92 −2.09 (m, 2H), 2.15 (ddd, *J*=13.3, 10.0, 8.6, 1H), 2.47 (ddd, *J*=18.8, 10.0, 8.6, 1H), 2.58 (ddd, *J*=18.8, 8.6, 2.0, 1H), 3.19 (dt, *J*=1.7, 5.7 Hz, 1H), 3.56 (d, *J*=14.3 Hz, 1H), 3.66 (s, 3H), 3.79 (s, 3H), 5.53 (d, *J*=14.3 Hz, 1H), 6.52 (q, *J*=1.5 Hz, 1H), 6.77−6.80 (m, 2H), 7.14 −7.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.3 (CH_3), 13.6 (CH_3), 24.0 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 48.6 (CH_2), 51.9 (CH_3), 55.2 (CH_3), 63.8 (CH), 71.6 (qC), 113.8 (CH), 128.4 (qC), 130.5 (qC), 132.3 (CH), 142.0 (CH), 159.1 (qC), 168.1 (CO), 168.6 (CO); MS (ESI) *m*/*z*: 384 (M+Na$^+$, 100%); IR (film) ν_{max}: 3346, 2957, 1715, 1618, 1509, 1459, 1252, 1030 cm^{-1}. HRMS (ESI) calcd for [$C_{20}H_{27}NO_5$+Na$^+$]: 384.1787; found 384.1782.

(2*R*,3'*S*,8a'*S*)-3'-((*tert*-Butyldiphenylsilyloxy)methyl)-4-methylenetetrahydro-1'*H*,3*H*-spiro[furan-2,8'-indolizine]-5,5'(4*H*,8a'*H*)-dione (16)

To a solution of hydroxyindolizidone derivative **15** (423 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) were added 4 Å molecular sieves (423 mg), NMO (292 mg, 2.5 mmol) and TPAP (35.1 mg, 0.1 mmol). The resultant mixture was stirred at room temperature for 50 min. The mixture was concentrated under reduced pressure and the residue was filtered through an Al_2O_3 pad eluting with ether. The solvent was removed under reduced pressure to afford the crude ketone, which was used in the next step without further purification. To a stirred solution of the

above obtained ketone in dry THF (8 mL) under N_2 atmosphere, Zn (195 mg, 3.0 mmol) was added. The mixture was heated to reflux, and a solution of ethyl-2-bromomethacrylate (0.2 mL, 1.5 mmol) in dry THF (2 mL) was added. After 1 h of refluxing, the ketone disappeared as indicated by TLC analysis. The mixture was filtered through Celite and the filtrate was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with a saturated NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2 (5 mL×2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Purification of the crude material by flash column chromatography on silica gel eluting with EtOAc/PE (2∶1) afforded compound **16** (445 mg, yield: 91%) as a white solid. m.p. 120−128 ℃ (MeOH); $[\alpha]_D^{20}$ −71 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.59−1.69 (m, 1H), 1.83−1.92 (m, 2H), 1.97−2.10 (m, 4H), 2.37 (dd, *J*=18.2, 6.3 Hz, 1H), 2.57 (ddd, *J*=18.2, 12.5, 7.0 Hz, 1H), 2.73 (dt, *J*=17.4, 3.0 Hz, 1H), 2.83 (dt, *J*=17.4, 2.8 Hz, 1H), 3.65 (dd, *J*=10.7, 5.6 Hz, 1H), 3.76 (dd, *J*=10.3, 2.3 Hz, 1H), 4.15 (dd, *J*=10.3, 4.0 Hz, 1H), 4.23—4.30 (m, 1H), 5.69 (t, *J*=2.6 Hz, 1H), 6.29 (t, *J*=3.0 Hz, 1H), 7.33—7.42 (m, 6H), 7.58—7.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.4 (C), 24.0 (CH_2), 25.3 (CH_2), 27.0 (CH), 28.2 (CH_2), 30.0 (CH_2), 33.6 (CH_2), 36.6 (CH_2), 58.4 (CH), 64.3 (CH_2), 66.0 (CH), 78.8 (C), 123.6 (CH_2), 127.69 (CH), 127.71 (CH), 129.7 (CH), 129.8 (CH), 133.5 (C), 133.6 (C), 135.49 (CH), 167.1 (CO), 169.0 (CO); IR (film) ν_{max}: 3070, 2959, 2930, 1769, 1582, 1426, 1267, 1066 cm^{-1}. HRMS (ESI) calcd for $[C_{29}H_{35}NO_4Si+Na^+]$: 512.2228; found 512.2230.

(2*R*,3'*S*,8a'*S*)-3'-(Hydroxymethyl)-4-methylenetetrahydro-1'*H*,3*H*-spiro[furan-2,8'-indolizine]-5,5'(4*H*,8a'*H*)-dione (17)

To a cooled solution (0 ℃) of compound **16** (110 mg, 0.23 mmol) in anhydrous THF (2 mL) under N_2 was added Py•HF (0.21 mL, 2.3 mmol) dropwise. After being stirred at room temperature for 24 h, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/MeOH (15∶1) to afford compound **17** (52 mg, yield: 92%) as a white solid. m.p. 145−146 ℃ (MeOH); $[\alpha]_D^{20}$ −42 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34−1.44 (m, 1H), 1.55−1.66 (m, 1H), 1.83 (td, *J*=12.1, 6.1 Hz, 1H), 1.98−2.14 (m, 3H), 2.51 (ddd, *J*=18.5, 5.4, 3.0 Hz, 1H), 2.62 (ddd, *J*=18.5, 11.7, 7.8 Hz, 1H), 2.79 (dt, *J*=17.5, 2.7 Hz, 1H), 2.87 (dt, *J*=17.5, 2.7 Hz, 1H), 3.50 (dd, *J*=11.6, 7.7 Hz, 1H), 3.63 (dd, *J*=11.5, 5.1 Hz, 1H), 3.68 (d, *J*=11.5 Hz, 1H), 5.35 (s, 1H), 5.70 (t, *J*=2.5 Hz, 1H), 6.28 (t, *J*=2.8 Hz, 1H), 7.58−7.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.8 (CH), 25.4 (CH), 28.1 (CH), 33.2 (CH), 36.4 (CH), 62.0 (CH_2), 66.0 (CH_2), 67.0 (CH), 60.0 (CH), 78.6 (C), 123.0 (CH), 133.2 (C), 168.8 (CO), 170.3 (CO); IR (film) ν_{max}: 3407, 2917, 2849, 1767, 1620, 1452, 1414, 1289, 1215, 1069 cm^{-1}. HRMS (ESI) calcd for $[C_{13}H_{17}NO_4+Na^+]$: 274.1050; found 274.1053.

((2*R*,3'*S*,8a'*S*)-4-Methylene-5,5'-dioxooctahydro-1'*H*,3*H*-spiro[furan-2,8'-indolizine]-3'-yl)methyl-4-nitrobenzenesulfonate (18)

To an ice-bath cooled solution of **17** (30 mg, 0.13 mmol) in CH_2Cl_2 (6 mL) were added successively DMAP (cat.), 4-nitrobenzene-1-sulfonyl chloride (86 mg, 0.39 mmol) and Et_3N (0.07 mL, 0.52 mmol). After being stirred at room temperature overnight, the reaction was quenched with a saturated aqueous $NaHCO_3$ (2 mL) and water (1 mL) at 0 ℃. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (6∶1) to afford compound **18** (50 mg, yield 96%) as a white solid. m.p. 160−161 ℃ (MeOH); $[\alpha]_D^{20}$ −56 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.82−1.95 (m, 2H), 1.55−1.66 (m, 1H), 1.97−2.16 (m, 3H), 2.38 (dd, *J*=18.4, 6.2 Hz, 1H), 2.56 (ddd, *J*=18.4, 12.0, 7.4 Hz, 1H), 2.80 (dt, *J*=17.5, 2.7 Hz, 1H), 2.88 (dt, *J*=17.5, 2.8 Hz, 1H), 3.66 (dd, *J*=10.9, 5.0 Hz, 1H), 4.18 (dd, *J*=10.1, 2.3 Hz, 1H), 4.21−4.30 (m, 1H), 4.63 (dd, *J*=10.1, 3.9 Hz, 1H), 5.72 (t, *J*=2.5 Hz, 1H), 6.30 (t, *J*=2.8 Hz, 1H), 8.05−8.10 (m, 2H), 8.36−8.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.2 (CH_2), 25.0 (CH_2), 28.1 (CH_2), 33.4 (CH2), 36.4 (CH_2), 56.1 (CH), 35.1 (CH_2), 65.7 (CH), 71.2 (CH_2), 78.5 (C), 124.1 (CH2), 124.6 (CH), 129.3 (CH), 133.1 (C), 141.4 (C), 151.0 (C), 168.1 (CO), 168.8 (CO); IR (film) ν_{max}: 3104, 2963, 2917, 2847, 1759, 1640, 1630, 1530, 1451, 1404, 1352, 1271, 1185, 1095 cm^{-1}. HRMS (ESI) calcd for $[C_{19}H_{20}N_2O_8S+Na^+]$: 459.0833; found 459.0836.

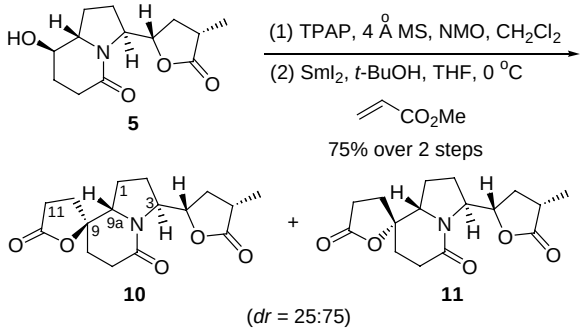
Results and Discussion

The SmI_2-mediated[10] reductive coupling-lactonization method[11] was first investigated. The hydroxyindolizidinone core **5**[7] found in sessilifoliamide J was chosen as a model substrate, which was converted to ketone **6** by Ley oxidation[12] (TPAP/NMO/4 Å MS). To confirm the *syn*/*anti* diastereoselectivity (C-9/C-9a)[8] in the subsequent spirolactonization, the SmI_2-mediated coupling of ketone **6** with methyl acrylate was first undertaken. The 11-demethyl derivative of sessilifoliamide J was obtained as a diastereomeric mixture (**10** and **11**) in a ratio of 25∶75 (determined by ^{1}H NMR) (Scheme 2). The two diastereomers could be separated by preparative HPLC. The stereochemistries of the two diastereomers were determined by NOESY experiments. The observed NOESY correlations between $H_{10\beta}\leftrightarrow H_{9a}\leftrightarrow H_{10\alpha}$ in compound **11** (Figure 2) allowed an unambiguous assignment of the stereochemistry of **11** as *anti* (C-9/C-9a). Thus the major diastereomer is 9-*epi*-11-demethylsessilifoliamide J (**11**) and the minor diastereomer is 11-demethylsessilifoliamide J (**10**). The results are in agreement with our previous observation

CHINESE JOURNAL OF CHEMISTRY

(cf. Scheme 1).[7]

Scheme 2 Ley oxidation-SmI_2-mediated tandem reductive coupling-lactonization



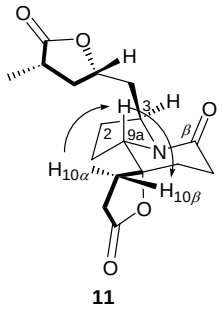
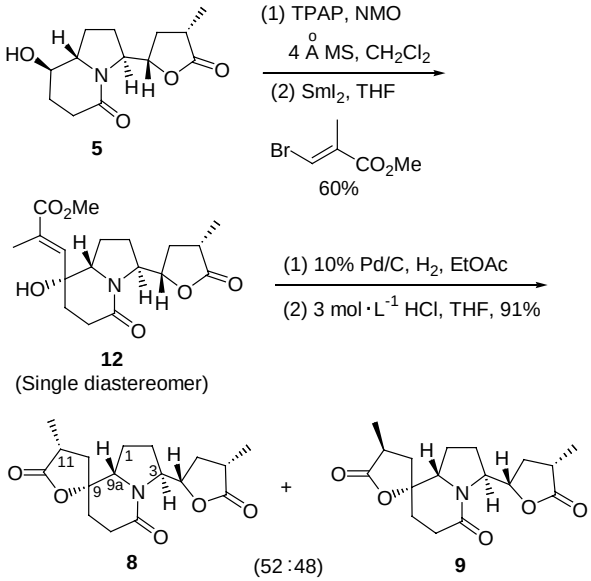


Figure 2 Observed key NOE correlations of the major diastereomer **11**.

To improve the diastereoselectivity in the spirolactonization reaction, a stereochemical control by introducing bromine atom as the stereodirecting group was envisaged. In the Evans asymmetric aldol methodology,[13] haloacetyloxazolidinone or methylthioacetyloxazolidinone has been used to overcome the low diastereoselectivity of the aldol reaction of acetyloxazolidinone. In those asymmetric aldol-type reactions, either chlorine or bromine atom or methylthio group served as a stereodirecting group and could be removed after the reaction. Herein we adopted the same tactic to improve the diastereoselectivity at C-9. Methyl (*E*)-3-bromo-2-methacrylate was thus selected as the coupling reagent. It was expected that the bromo atom served firstly as a stereodirecting group in the coupling reaction with ketone **6**, then *β*-elimination occurred spontaneously to give a butenolide, which in turn could be subjected to asymmetric hydrogenation to establish the stereogenic centre at C-11.

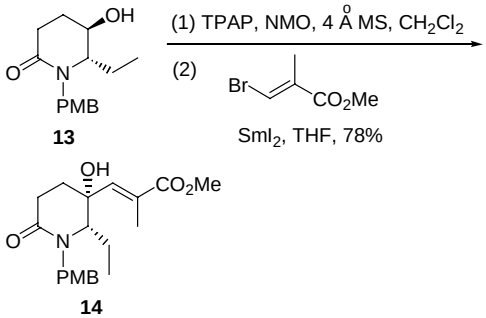
To our delight, Ley oxidation of compound **5** followed by treatment of the resulting ketone with SmI_2 and methyl (*E*)-3-bromo-2-methacrylate afforded compound **12** as a single diastereomer (Scheme 3). The geometry of the olefin could not be determined by NOESY due to an overlap of the signals, however, it could be deduced to be *E*-form based on the fact of failing to form the butenolide under the reaction conditions. Catalytic hydrogenation [10% Pd/C, H_2 (1 atm), EtOAc] followed by treatment of the reduction product with a solution of HCl in THF (3 mol•L^{-1}) gave diastereomers **8** and **9** in a ratio of 52∶48. Use of other reducing conditions such as catalytic hydrogenation by Crabtree's catalyst,[14] and $NiCl_2/NaBH_4$ in MeOH[15] did not improve the diastereoselectivity at C-11. Comparing the ^1H and ^{13}C NMR spectra of two products with those we reported previously[7] came to a conclusion that the products are actually (−)-9-*epi*-sessilifoliamide J (**8**) and (−)-9,11-di-*epi*-sessilifoliamide J (**9**), respectively. Although we were unable to establish the *syn*-stereochemistry (C-9/C-9a) of sessilifoliamide J, the *anti*-stereochemistry (C-9/C-9a) found in other *Stemona* alkaloids could be established in excellent diastereoselectivity by using bromine atom as a directing element.

Scheme 3 Ley oxidation-SmI_2-mediated reductive coupling and subsequent lactonization



To further test the bromo-directed diastereoselective reductive coupling reaction, 6-ethyl-5-hydroxypiperidin-2-one **13** was oxidized with the Ley reagent and the resulting ketone was subjected to the SmI_2-mediated reductive coupling with methyl (*E*)-3-bromo-2-methacrylate. *trans*-Diastereomer **14** was obtained again as a single diastereomer (Scheme 4).

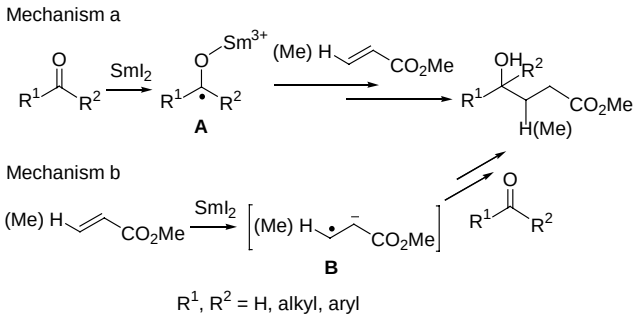
Scheme 4 Ley oxidation-SmI_2-mediated reductive coupling of compound **13**



The role of the bromine atom in the diastereoselective reductive coupling reaction deserves comment. For the SmI_2-mediated coupling of aldehydes and *α*,*β*-unsa-

turated esters leading to γ-butyrolactones, mechanisms involving either the first reduction of an aldehyde to a ketyl-radical anion **A** (mechanism a)[16] or the first reduction of an α,β-unsaturated ester to a radical-anionic intermediate **B** (mechanism b)[17] have been postulated, respectively, by Procter (Scheme 5).

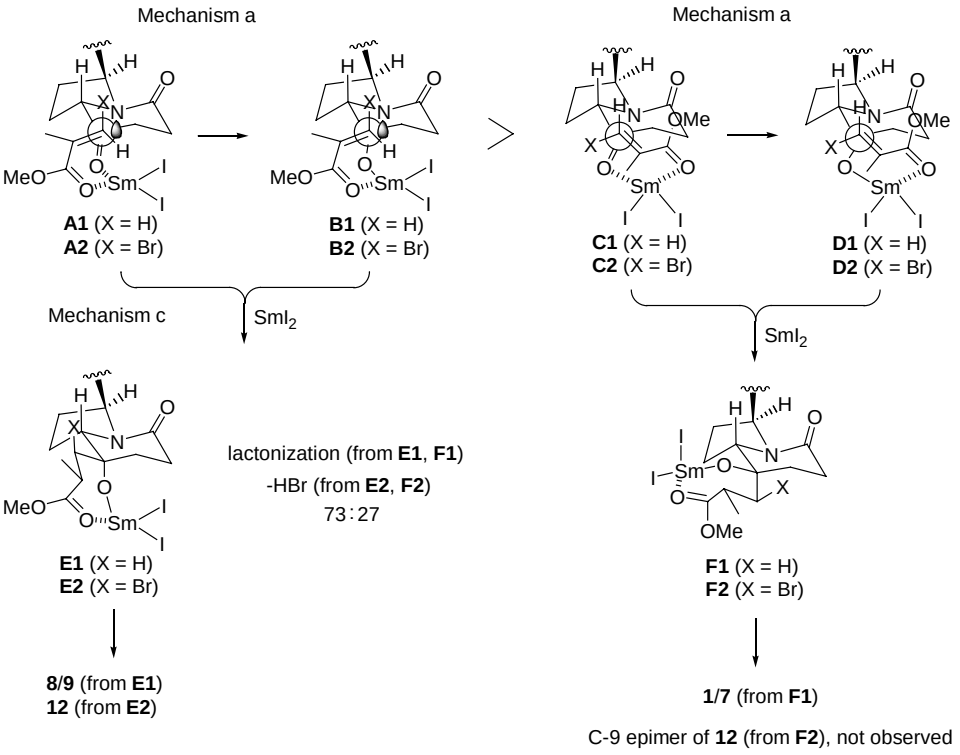
Scheme 5 Two mechanisms proposed by Procter



It occurs to us that a chelation enhanced sequential single electron transfer mechanism (mechanism c) can not be excluded. On the basis of these considerations, a plausible stereochemical course of the diastereoselective coupling reactions (Schemes 2 and 3) is depicted in Scheme 6. The initial chelating conformers could be represented by **A1** (X=H)/**A2** (X=Br) versus **C1** (X=H)/**C2** (X=Br), which are valuable for mechanisms a—c (mechanism b no shown in Scheme 6). The first single electron transfer from SmI_2 gives the corresponding ketyl-radical anions **B1**/**B2** or **D**/**D2**, respectively. The subsequent addition of the ketyl-radical anion to α,β-unsaturated esters gives **E1**/**E2** or **F1**/**F2**, respectively (mechanism a). Alternatively, due to the higher reactivity of both methyl (*E*)-methacrylate and methyl (*E*)-3-bromo-2-methacrylate, the SmI_2-mediated coupling reaction might pass through a sequential single electron transfer manner to give directly **E1**/**E2** or **F1**/**F2** (mechanism c). The conformations **A1,2**/**B1,2** featured the disposition of the olefin moiety at the equatorial position are less congested (and are thus more stable) comparing with **C1**,**2**/**D1**,**2**. This can account for the formation of epimers **8**/**9** as the major diastereomers. For conformations **A2** and **B2**, further stabilization effect gains from orbital interaction between perpenticularly oriented C—Br bond (σ*-orbital) and C=O (π-orbital) bond or •C—O^- bond. In addition, the perpenticularly disposed dipole of C—Br bond and the nitrogen lone pair might provide yet additional stabilization effect to the conformations **A2**/**B2**; while such beneficial effects do not exist in conformations **A1**/**B1**, **C1**,**2**/**D1**,**2**. Consequently, compound **12** was obtained as the sole observable diastereomer, while the C-9 epimer of **12** was no observed.

We next investigated the organozinc reagent-based one-pot lactonization method.[18] The hydroxyindolizidinone **15**,[9] which was easily available from (*S*)-pyroglutamic acid via the vinylogous Mannich reaction (VMR),[19] was oxidized by the Ley oxidation. The following reaction of the resulting ketone with zinc re-

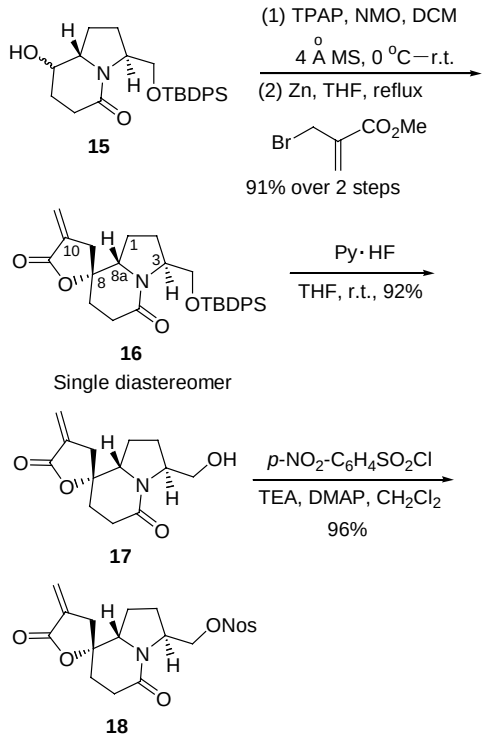
Scheme 6 Plausible stereochemical course of the diastereoselective coupling reaction



CHINESE JOURNAL OF CHEMISTRY

agent generated from methyl bromomethacrylate gave the spiro-α-methylene-γ-lactone **16** as the only observable diastereomer in 91% over two steps. Desilylation (Py•HF 10 equiv., THF, r.t.) of silyl ether **16** gave compound **17** in 92% yield. Treatment of alcohol **17** with p-$NO_2C_6H_4SO_2Cl$ (TEA, DMAP, CH_2Cl_2) gave crystalline compound **18**, which was subjected to single crystal X-ray diffraction analysis (Figure 3). The stereochemistry of spiro-α-methylene-γ-lactones **16** and **17** was thus established as *anti*. Although this complete facial selective lactonization method has been reported in the synthesis of the putative structure of *Stemona* alkaloid stemonidine,[20] the result is still remarkable because a substrate without any stereodirecting group such as an α-methoxy group[20] or an α-hydroxyl group is involved.[21]

Scheme 7 Organozinc reagent-based one-pot lactonization



Conclusions

We have demonstrated that by using bromine atom as a traceless directing group, the SmI_2-mediated reductive coupling of ketone **6** and β-bromo-methacrylate could proceed with complete *anti*-diastereoselectivity. To the best of our knowledge, this is the first example of applying the halo-directing tactic in the SmI_2-mediated reductive coupling of ketone with acrylate.

We also showed that without the presence of any α-directing (chelation) group, the one-pot reaction of the ketone derived from alcohol **15** with the organozinc reagent generated from bromomethacrylate afforded spiro-α-methylene-γ-lactone **16** as a single diastereomer.

These two highly diastereoselective methods would find application in the synthesis of the spirolactone/pyrrolidine moieties of some *Stemona* alkaloids with *anti*-configuration.

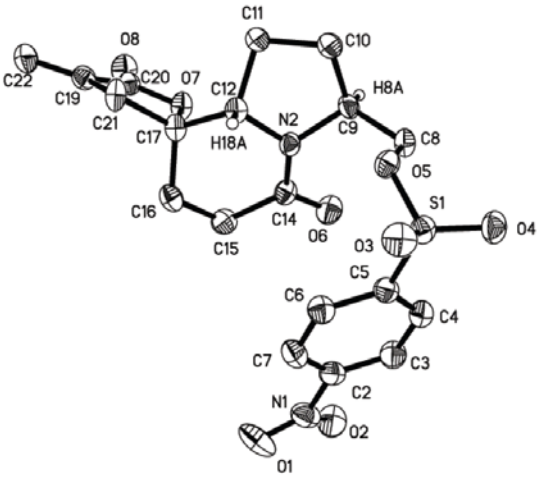


Figure 3 X-ray structure of compound **18**.

In addition, on the basis of our previous work,[7,9] we have accomplished the total synthesis of (−)-9-*epi*-11-demethylsessilifoliamide J (**11**) and an improved synthesis of (−)-9,11-di-*epi*-sessilifoliamide J (**9**).

Acknowledgement

The authors are grateful for financial support from the National Basic Research Program (973 Program) of China (Grant No. 2010CB833200), the NSF of China (21072160; 20832005), the Fundamental Research Funds for the Central Universities of China (Grant No. 201112G001).

References

[1] Trost, B. M. *Science* **1991**, *254*, 1471.
[2] de Vries, J. G.; Molander, G. A.; Evans, P. A. *Science of Synthesis Workbench Edition*: *Stereoselective Synthesis*, Vols. 1—3, Thieme, New York, Stuttgart and Delhi, **2011**.
[3] For a review on the synthesis of lactones, see: (a) Paryzek, Z.; Skiera, I. *Org. Prep. Proceed. Int.* **2007**, *39*, 203; For a review on the synthesis of spiro-lactones, see: (b) Bartoli, A.; Rodier, F.; Commeiras, L.; Parrain, J.-L.; Chouraqui, G. *Nat. Prod. Rep.* **2011**, *28*, 763.
[4] For reviews, see: (a) Pilli, R. A.; Rosso, G. B.; De Oliveira, M. d. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117; (b) Greger, H. *Planta Med.* **2006**, *72*, 99; (c) Alibés, R.; Figueredo, M. *Eur. J. Org. Chem.* **2009**, 2421; (d) Pilli, R. A.; Rosso, G. B.; De Oliveira, M. d. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908.
[5] Hitotsuyanagi, Y.; Takeda, E.; Fukaya, H.; Takeya, K. *Tetrahedron Lett.* **2008**, *49*, 7376.
[6] For an account, see: (a) Huang, P.-Q. *Synlett* **2006**, 1133; For selected recent examples, see: (b) Fu, R.; Ye, J.-L.; Dai, X.-J.; Ruan, Y.-P.; Huang, P.-Q. *J. Org. Chem.* **2010**, *75*, 4230; (c) Zhang, H.-K.; Lin, Z.-J.; Huang, H.; Huo, H.-H.; Huang, Y.-J.; Ye, J.-L.; Huang, P.-Q. *Chin. J. Chem.* **2010**, *28*, 1717; (d) Yang, R.-F.; Huang, P.-Q. *Chem.-Eur. J.* **2010**, *16*, 10319; (e) Lin, G.-J.; Zheng, X.; Huang, P.-Q *Chem. Commun.* **2011**, 1545; (f) Du, Y.; Huang, H.-Y.; Liu, H.; Ruan, Y.-P.; Huang, P.-Q. *Synlett* **2011**, 565; (g) Zhang, H.-K.; Li, X.; Huang, H.; Huang, P.-Q. *Scientia Sinica Chim.* **2011**, *41*, 732 (in Chinese); *Sci. China Chem.* **2011**, *54*, 737; (h) Liu, X.-K.; Qiu, S.; Xiang, Y.-G.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. *J. Org. Chem.*

2011, *76*, 4952; (i) Yang, C.; Bao, Y.-H.; Liang, P.; Ye, J.-L.; Wang, A.-E; Huang, P.-Q. *Tetrahedron* **2011**, *67*, 6281; (j) Chen, G.-Y.; Huang, H.; Ye, J.-L.; Huang, H.-Y.; Ruan, Y.-P.; Wang, A.-E; Huang, P.-Q. *Chem*. *Asian J*. **2012**, *7*, 504.

[7] Tuo, S.-C.; Ye, J.-L.; Wang, A.-E; Huang, S.-Y.; Huang, P.-Q. *Org*. *Lett*. **2011**, *13*, 5270.

[8] Carbon numbered according to reference [5].

[9] Liu, X.-K.; Ye, J.-L.; Ruan, Y.-P.; Li, Y.-X.; Huang, P.-Q. *J*. *Org*. *Chem*. **2012**, *77*, DOI: 10. 1021/jo3014484.

[10] For a recent book on application of SmI_2 in organic synthesis, see: (a) Procter, D. J.; Flowers, R. A.; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide*: *A Practical Guide*, Royal Society of Chemistry, Cambridge, **2010**; For reviews on SmI_2, see: (b) Namy, J. L.; Girard, P.; Kagan, H. B. *New*. *J*. *Chem*. **1977**, *1*, 5; (c) Girard, P.; Namy, J. L.; Kagan, H. B. *J*. *Am*. *Chem*. *Soc*. **1980**, *102*, 2693; (d) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351; (e) Gopalaiah, K.; Kagan, H. B. *New*. *J*. *Chem*. **2008**, *32*, 607; (f) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew*. *Chem*., *Int*. *Ed*. **2009**, *48*, 7140.

[11] (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett*. **1986**, *27*, 5763; (b) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J*. *Chem*. *Soc*., *Chem*. *Commun*. **1986**, 624; (c) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J*. *Chem*. *Soc*., *Perkin Trans*. *1* **1988**, 1669; (d) Inanaga, J.; Ujikawa, O.; Handa, Y.; Otsubo, K.; Yamaguchi, M. *J*. *Alloys Compd*. **1993**, *192*, 197; (e) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J*. *Org*. *Chem*. **1994**, *59*, 6900; (f) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373; (g) Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J*. *Am*. *Chem*. *Soc*. **1997**, *119*, 1482; (h) Matsuda, F.; Kawatsura, M.; Dekura, F.; Shirahama, H. *J*. *Chem*. *Soc*., *Perkin Trans*. *1* **1999**, 2371; (i) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J*. *Org*. *Chem*. **2001**, *66*, 3953; (j) Fukuzawa, S.-i.; Miura, M.; Saitoh, T. *J*. *Org*. *Chem*. **2003**, *68*, 2042.

[12] (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J*. *Chem*. *Soc*., *Chem*. *Commun*. **1987**, 1625; (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

[13] For the use of halogen as a stereodirecting group for the asymmetric ethoxycarbonylmethylation, see: (a) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett*. **1987**, *28*, 39; For applications of this methodology, see: (b) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J*. *Am*. *Chem*. *Soc*. **1999**, *121*, 7540; (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J*. *Am*. *Chem*. *Soc*. **2000**, *122*, 10033; (d) Yu, D.-S.; Xu, W.-X.; Liu, L.-X.; Huang, P.-Q. *Synlett* **2008**, 1189.

[14] (a) Crabtree, R. *Acc*. *Chem*. *Res*. **1979**, *12*, 331; (b) Stork, G.; Kahne, D. E. *J*. *Am*. *Chem*. *Soc*. **1983**, *105*, 1072; (c) Crabtree, R.; Davis, M. W. *J*. *Org*. *Chem*. **1986**, *51*, 2655; (d) Evans, D. A.; Kværnø, L.; Dunn, T. B.; Beauchemin, A.; Raymer, B.; Mulder, J. A.; Olhava, E. J.; Juhl, M.; Kagechika, K; Favor, D. A. *J*. *Am*. *Chem*. *Soc*. **2008**, *130*, 16295; (e) Gao, S.-H.; Wang, Q.-L.; Chen, C. *J*. *Am*. *Chem*. *Soc*. **2009**, *131*, 1410.

[15] Satoh, T.; Nanba, K.; Suzuki, S. *Chem*. *Pharm*. *Bull*. **1971**, *19*, 817.

[16] Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org*. *Biomol*. *Chem*. **2004**, *2*, 2476.

[17] (a) Johnston, D.; Couché, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org*. *Biomol*. *Chem*. **2003**, *1*, 328; (b) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org*. *Lett*. **2003**, *5*, 4811; (c) Vogel, J. C.; Butler, R.; Procter, D. J. *Tetrahedron* **2008**, *64*, 11876.

[18] Rollin, Y.; Derien, S.; Duńach, E.; Gebehenne, C.; Perichon, J. *Tetrahedron* **1993**, *49*, 7723.

[19] For reviews/accounts on vinylogous Mannich reactions, see: (a) Martin, S. F. *Pure Appl*. *Chem*. **1997**, *69*, 571; (b) Arend, M.; Westermann, B.; Risch, N. *Angew*. *Chem*., *Int*. *Ed*. **1998**, *37*, 1044; (c) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem*. *Rev*. **2000**, *100*, 1929; (d) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221; (e) Martin, S. F. *Acc*. *Chem*. *Res*. **2002**, *35*, 895.

[20] Sánchez-Izquierdo, F.; Blanco, P.; Busqué, F.; Alibés, R.; De March, P.; Figueredo, M.; Font, J.; Parella, T. *Org*. *Lett*. **2007**, *9*, 1769.

[21] Sawant, M. S.; Katoch, R.; Trivedi, G. K.; Desai, U. R. *J*. *Chem*. *Soc*., *Perkin Trans*. *1* **1998**, 843.

(Pan, B.; Fan, Y.)

