HETEROCYCLES, Vol. 55, No. 8, pp. 1505 - 1518, Received, 6th June, 2001

A NEW ASYMMETRIC SYNTHESIS OF (*R*)-3-METHYLPYRROLIDINE ALKALOIDS STARTING FROM (*S*)-MALIC ACID

Xiao Zheng,[b] Pei Qiang Huang,[a, b *] Yuan Ping Ruan, [b] Albert W. M. Lee,[c] and Wing Hong Chan[c]

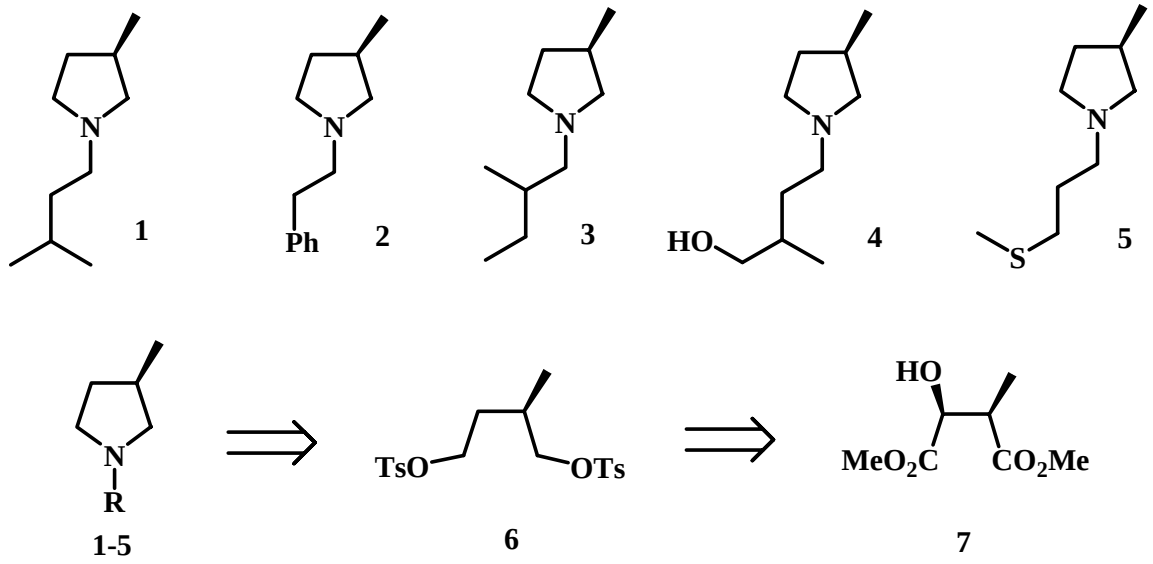
[a] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China
[b]Department of Chemistry, Xiamen University, Xiamen 361005, P. R. China
[c] Department of Chemistry, Hong Kong Baptist University, Hong Kong, P. R. China

Abstract --- Diastereoselective methylation of dimethyl (*S*)-malate (**8**) followed by two three-step reductive dehydroxylation procedures afforded dimethyl (*R*)-2-methylsuccinate (**16**) in 80.2% and 84.7% ee respectively, the later was further transformed into the natural enantiomers of ant venom alkaloids (*R*)-leptothoracine (**1**) and (*R*)-3-methyl-*N*-(2-phenylethyl)pyrrolidine (**2**) and (3*R*, 2'*S*)-3-methyl-*N*-(2-methylbutyl)pyrrolidine (**3**).

Substituted pyrrolidine moiety is found in a large number of naturally occurring pyrrolidine, pyrrolizidine, indolizidine and tropane alkaloids. Most of them are either ant venom alkaloids[1] or alkaloids extracted from the skin of neotropical poison frogs,[2] which are characterized by the presence of *trans*-2,5-disubstituted pyrrolidine skeleton,[3] other substituted pyrrolidine is relatively rare. In 1995, Veith *et al*. reported[4] the isolation of five *N*-alkylated 3-methylpyrrolidine (**1-5**), the same group reported their absolute configurations.[5] Since then, a racemic synthesis,[4] a chiral synthesis[6] and one asymmetric synthesis[7] have been reported. In connection with a program aiming at the development of (*S*)-malic acid–based methodology,[8] we would like to report herein a new asymmetric synthesis of these alkaloids.

As shown in **Scheme 1**, a simple retrosynthetic analysis implicates methyl (2*S*, 3*R*)-3-methylmalate (**7**) as a key intermediate which could be obtained by methylation of dimethyl (*S*)-malate (**8**).

The synthesis of the requisite (*R*)-2-methyl-1,4-butanediol (**17**) began with the esterification (MeOH, $SOCl_2$, room temperature, 36 h) of easily available (*S*)-malic acid. Methylation[9] of dimethyl (*S*)-malate

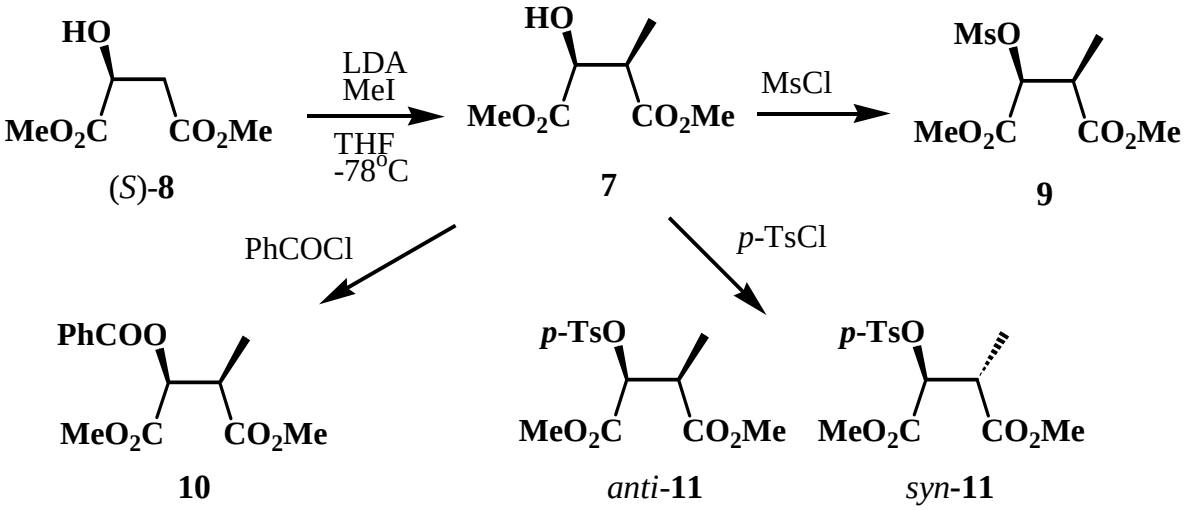


Scheme 1

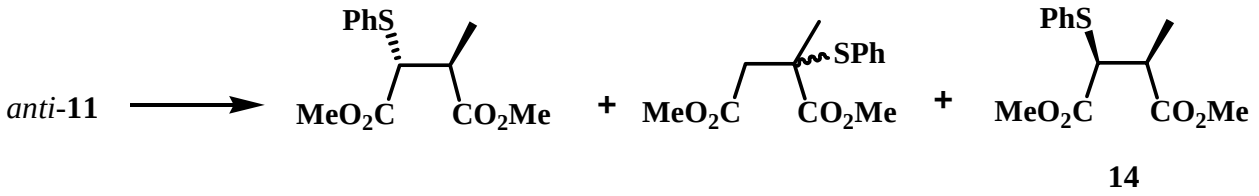
(2.2 equiv., LDA, MeI, THF, -78°C, 40 h) (**Scheme 2**) led to an inseparable diastereomeric mixture of dimethyl (2*S*, 3*R*)- and (2*S*, 3*S*)-3-methylmalates[9] in which the desired *anti*-isomer (**7**) predominated (de=79.8% as indicated by ^{1}H-NMR, combined yield 72%). Since the diastereomers (**7**) will become inseparable enantiomers after cleavage of hydroxyl group, the separation of minor diastereomer from the enriched diastereomeric mixture of **7** (only *anti*-isomer is showed in **Scheme 2**) *via* derivatizaion is necessary. For this purpose, mesylate (**9**), benzoate (**10**) and tosylate (**11**) were prepared respectively from **7**. Although mesylate (**9**) and benzoate (**10**) were still inseparable by flash chromatography, the diastereomeric tosylates (**11**) turned out to be separable by flash chromatography.

After serving as a valuable derivative for diastereomer separation, the second role of the tosyloxy group in **11** is as a leaving group. The displacement of tosyloxy group by thiophenol merits some comments. As shown in **Scheme 3** (**Method A**), the reaction of lithium thiophenolate at -10°C-0°C (**method 1**, PhSLi / THF, -10°C-0°C) gave disappointing low selectivity, a total of three products (**12-14**) can be isolated and/or observed by ^{1}H-NMR (**12** and **13** are inseparable by column chromatography). The structure of two minor products was tentatively assigned as **13** and **14**. The formation of **13** and **14** might implicate that during the formation of **12**, the desired S_N2 substitution reaction is accompanied by elimination reaction leading to the formation of dimethyl 2-methylfumarate (**15**). Subsequent reaction of thiophenolate with dimethyl 2-methylfumarate (**15**) would lead to a total of six regio- and stereoisomers (**12-14**), including the antipode of **12**. However, since compound (**14**) is optically active, this might implicates that the epimerization of **12** contributed as well to the formation of **14**. Fortunately, the reaction of potassium thiophenolate with tosylate (**11**) (**method 2**) was showed to be much more selective. Further improvement of the combined yield resided on the direct treatment of

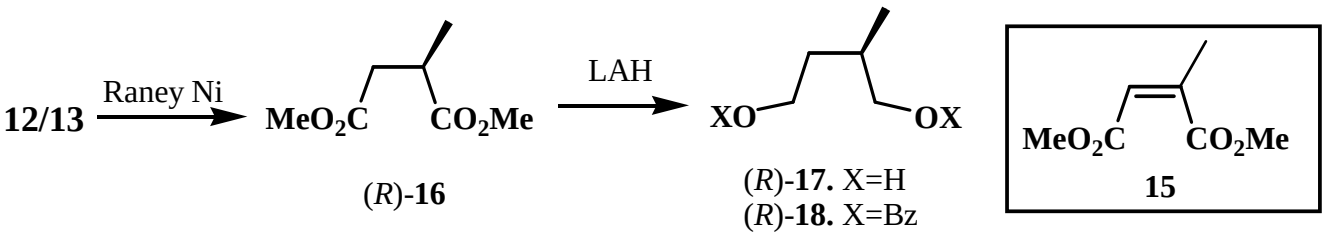
thiophenol with tosylate (**11**) in the presence of potassium carbonate (**method 3**), the total yield was 90%.



Scheme 2



Method 1.	PhSLi / THF, -10°C~0°C	**12** : **13** : **14** = 36 : 24 : 40	combined yield 71%
Method 2.	PhSK / EtOH, rt	**12** : **13** : **14** = 90 : 5 : 5	combined yield 84%
Method 3.	PhSH / K_2CO_3 / Et_2O, 5°C	**12** : **1 3**: **14** = 90 : 5 : 5	combined yield 90%

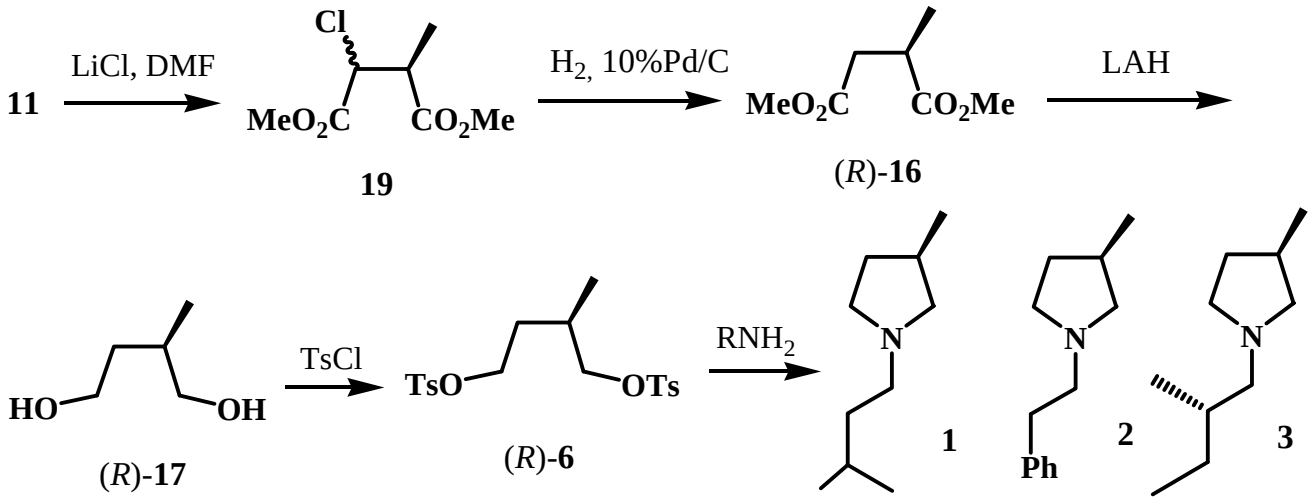


Scheme 3 (**Method A**)

Since **12** and **13** are inseparable by column chromatography, this mixture (in a ratio of 94.7 : 5.3) was subjected directly to Raney Nickel desulfidation (room temperature, 12 h), the reaction ran smoothly, affording the desired dimethyl (*R*)-methyl succinate (**16**)[10] [80.2% ee as indicated by chiral HPLC analysis of **18**[11]] in a yield of 97%. The observed modest enantiomeric excess of **16** confirmed the mechanism considerations mentioned above, namely, the modest ee is due to the presence of both

racemic **13** and a small portion of antipode of **12**.

In order to improve the enantiomeric excess of diester (**16**), an alternative approach (**Scheme 4**, **Method B**) was exploited. Thus, the reaction of anhydrous LiCl with tosylate (**11**) in hot dry DMF for 9 h yielded chloride (**19**) as a mixture of two inseparable diastereomers (combined yield 76%). The diastereomeric ratio is 53 : 47 as calculated from ^{1}H-NMR spectrum. The stereochemistry of isomeric **19** was not assigned. Although **19** can be dechlorinated to dimethyl (*R*)-methylsuccinate **(16**) under radical conditions, an environmentally friendly procedure was adopted to achieve the reductive dechlorination. To our delight, the hydrogenolysis (H_2, 10% Pd/C, NEt_3 MeOH, 6 h) of the diastereomeric mixture (**19**) afforded cleanly dimethyl (*R*)-methylsuccinate (**16**) in 89% yield. Since chloride **(19**) is volatile, care must take to avoid the evaporation of **19**, in such a way, the overall yield for the transformation of **11** to **16** is 81%.



Scheme 4 (**Method B**)

Lithium aluminium hydride reduction of **16** (LAH, THF, 0°C-rt, 6 h, 82%) then yielded known (*R*)-2-methyl-1,4-butanediol[6] (**17**) as a colorless oil { $[\alpha]_D^{20}$ +11.7° (*c* 1.92, MeOH), 84.7% ee; lit.,[12a] for (*R*-**17**): $[\alpha]_D^{22}$ +14.4° (*c* 2.0, MeOH); lit.,[6] $[\alpha]_D^{20}$ +9.42° (*c* 1.04, MeOH), 65% ee; lit.,[6] $[\alpha]_D^{20}$ +13.9° (*c* 1.35, MeOH), 97% ee; lit.,[12b] (*S*)-(**17**): $[\alpha]_D^{20}$ –14.4° (*c* 0.6, MeOH); lit.,[6] $[\alpha]_D^{20}$ –13.8° (*c* 1.24, MeOH), 96% ee}. The enantiomeric excess of diol (*R*-**17**) thus formed is 84.7 % as determined by chiral HPLC analysis of its dibenzoate derivative (**18**).[11] These results indicate that partial racemization occur during the transformation of diastereomeric pure **11** to **17**, since the conversion of **16** to **17** was performed under racemization free conditions.[6] The observed partial racemization might occur during the formation

of **19** or **16**.

Under the tosylation conditions (*p*-TsCl, Pyridine, DMAP, CH_2Cl_2, 0-5°C) diol (**17**) was ditosylated to give compound (*R*-**6**),[7] which upon treatment with 3-methylbutylamine at room temperature for 4 days afforded the desired natural enantiomer of ant venom alkaloid (*R*)-3-methyl-*N*-(3-methylbutyl)-pyrrolidine (leptothoracine) (**1**)[6, 7] {$[\alpha]_D^{20}$ –1.54° (*c* 0.95, EtOH), 84.7 % ee; lit.,[6] for (*R*-**1**): $[\alpha]_D^{20}$–1.80° (*c* 0.96, EtOH); (*S*-**1**): $[\alpha]_D^{20}$ +1.81° (*c* 3.03, EtOH)} in a yield of 66%. Similarly, the reaction of ditosylate (*R*-**6**) with 2-phenylethylamine afforded the expected alkaloid (*R*)-3-methyl-*N*-(2-phenylethyl)pyrrolidine (**2**)[7] { $[\alpha]_D^{20}$ –1.87° (*c* 0.99, EtOH), 84.7% ee} in excellent yields (96%). Finally, the reaction of *R*-**6** with (*S*)-(-)-2-methylbutylamine afforded **3** in a yield of 71%. The low yields of *R*-**1** and *R*-**3** compared with those of *R*-**2** might due to the volatility of pyrrolidine (**1**) and (**3**).

In conclusion, we have developed a new seven-step asymmetric synthesis of (*R*)-3-methylpyrrolidine alkaloids from available dimethyl (*S*)-malate. The overall yield for alkaloids (*R*-**1**), (*R*-**2**) and (*R*-**3**) is 15.9%, 23.1% and 17.1% respectively. The enantiomeric excess of the final products is 84.7%.

EXPERIMENTAL

IR spectra were measured with a Nicolet Avatar 360 FT-IR spectrophotometer using film NaCl techniques. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Varian unity + 500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. MS spectra were recorded by Finnigan Mat-LCQ (ESI direct injection). HRFABMS spectra were recorded on a Bruker APEX-II FTMS apparatus. Optical rotations were measured with Perkin-Elmer 341 automatic polarimeter. Elemental analyses were performed using a Vario EL III analyser. THF and ether used in the reactions were dried by distillation over metallic sodium and benzophenone; dichloromethane was distilled over P_2O_5. Silica gel (Zhifu, 300-400 mesh) from Yian-Tai Silica gel Factory (China) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60-90°C) mixtures. HPLC analyses were performed with a Chiralcel® OB column, eluting with hexane / *iso*-propanol (95/5, v/v) mixtures, on a Waters HPLC 510 instrument.

Dimethyl (2S, 3R)-3-methylmalate (7)

To a stirred cold solution of diisopropylamine (5.5 mL, 39.3 mmol) in THF (17 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexanes (22.6 mL, 36.1 mmol). The mixture was stirred at 0°C

for 15 min and then cooled to -78°C. A solution of dimethyl (*R*)-malate (2.99 g, 18.5 mmol) in THF (4.5 mL) was added dropwise (30 min). After stirred at -78°C for 1.5 h, methyl iodide (2.7 mL, 43.0 mmol) was added dropwise. The mixture was stirred at -78°C for 44 h, and then quenched by adding a solution of 3.70 g of glacial acetic acid in 5.0 mL of THF at -78°C. The resulting mixture was allowed to reach rt and then diluted by dichloromethane (200 mL). After careful addition of a saturated sodium bicarbonate (20 mL), the mixture was poured into a separatory funnel. The organic layer was washed successively with water (10 mL), a saturated solution of sodium bicarbonate (10 mL) and brine (10 mL), dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure followed by flash chromatographic purification on silica gel (eluent: EtOAc / PE = 1 : 2) afforded colorless liquid (**7**) [9a] (2.35 g, 72%) as an inseparable diastereomeric mixture (*anti* : *syn* = 89.9 : 10.1 as indicated by ^{1}H-NMR) as an oil. $[\alpha]_D^{20}$ –5.21°(*c* 1.52, Et_2O) {lit.,[9a,b] $[\alpha]_D^{20}$ –4.1° (*c* 1.035, ether), *anti*: *syn* = 91 : 1 determined by GC}. IR: 3496, 2985, 2956, 2887, 1743, 1438, 1382, 1210, 1142, 1103, 1069, 1047, 1008, 839, 802 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): major *anti*-isomer: δ 1.28 (d, *J* = 7.30 Hz, 3H, C3-CH_3), 3.02 (dq, *J* = 3.73, 7.30 Hz, 1H, H-3), 3.10-3.30 (br, s, 1H, -OH), 3.65 (s, 3H, $COOCH_3$), 3.78 (s, 3H, $COOCH_3$), 4.26 (d, *J* = 3.73 Hz, 1H, H-2) ppm; MS (ESI): 375.4 ($2M^+$+23, 42), 199.6 (M^++23, 100), 177.6 (M^++1, 22).

Dimethyl (2S, 3R)-3-methyl-2-O-mesylmalate (9)

To a solution of **7** (176 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (5 mL) were added successively triethylamine (0.42 mL, 3.0 mmol) and MsCl (0.25 mL, 3.0 mmol) at 0°C. After stirred at rt for 1 h, the reaction mixture was diluted with ether (10 mL) and stirring continued for 30 min. The mixture was filtered over celite, concentrated under reduced pressure and the residue was subjected to flash chromatographic purification (eluent: EtOAc: PE = 1 : 2) providing a colorless oily mixture of *anti*-**9** / *syn*-**9** isomers (232 mg, 92.7%, *anti : syn* = 89.9 : 10.1) as an oil. $[\alpha]_D^{20}$ –31.1° (*c* 0.96, $CHCl_3$). IR: 3103, 3022, 2995, 2957, 2851, 1739, 1652, 1437, 1361, 1207, 1175, 1050, 1019, 961, 834, 788, 734 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): major *anti*-isomer: 1.32 (d, *J* = 7.29 Hz, 3H, C3-CH_3), 3.19 (s, -SO_2CH_3), 3.22 (dq, *J* = 5.12, 7.29 Hz, 1H, H-3), 3.68 (s, 3H, $COOCH_3$), 3.84 (s, 3H, $COOCH_3$), 5.18 (d, *J* = 5.12 Hz, 1H, H-2). MS (ESI): 531.5 ($2M^+$+23, 100), 277 (M^++23, 20), 272 (M^++18, 40), 255 (M^++1, 9), 254 (M^+, 1). HRESIMS calcd for [$C_8H_{14}O_7S$+Na]$^+$: 277.0352; found: 277.0357.

Dimethyl (2S, 3R)-3-methyl-2-O-benzoylmalate (10)

To a mixture of **7** (210 mg, 1.19 mmol) and DMAP (cat.) in anhydrous CH_2Cl_2 (6.0 mL) were added successively triethylamine (0.124 mL, 1.67 mmol) and benzoyl chloride (0.17 mL, 1.43 mmol) at 0°C. After stirred at rt for 18 h, the reaction mixture was rechilled to 0°C, water (2 mL) was added, the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was washed successively with a 50% aqueous citric acid solution (2.0 mL) and brine (2.0 mL) and dried with anhydrous Na_2SO_4. After flash chromatographic purification (eluent: EtOAc / PE = 1 : 6), a colorless oily mixture of *anti*-**10** : *syn*-**10** isomers (289 mg, 86.5%, *anti : syn* = 89.9 : 10.1) were obtained. $[\alpha]_D^{20}$ –1.52° (*c* 1.30, $CHCl_3$). IR: 3064, 2993, 2954, 2848, 1732, 1601, 1584, 1454, 1436, 1360, 1259, 1110, 1027, 854, 833, 801, 760, 712, 687 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): major *anti*-isomer: 1.32 (d, *J* = 7.22 Hz, 3H, C3-CH_3), 3.28 (dq, *J* = 5.18, 7.22 Hz, 1H, H-3), 3.75 (s, 3H, $COOCH_3$), 3.80 (s, 3H, $COOCH_3$), 5.50 (d, *J* = 5.18 Hz, 1H, H-2), 7.44 (2H), 7.60 (1H), 8.00 (2H). MS (ESI): 303.9 (M^++23, 100). HRESIMS calcd for [$C_{14}H_{16}O_6$+Na]$^+$: 303.0839; found: 303.0845. Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.0; H, 5.7. Found: C, 59.8; H, 5.8.

Dimethyl (2S, 3R)-3-methyl-2-O-tosylmalate (11)

To a solution of **7** (140 mg, 0.79 mmol) in anhydrous CH_2Cl_2 (1 mL) were added successively pyridine (0.1 mL, 1.19 mmol), a solution of *p*-TsCl (182 mg, 0.95 mmol) in anhydrous CH_2Cl_2 (0.5 mL) and DMAP (cat.) at 0°C. After stirred at rt for 30 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and water, the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was washed successively with a saturated solution of $NaHCO_3$ (1.5 mL) and brine (1.5 mL) and dried with anhydrous Na_2SO_4. After flash chromatographic purification (eluent: EtOAc : PE = 1 : 3), pure *anti*-isomer (**11**) (yield, 50%) and a mixture of *anti*-**11** / *syn*-**11** isomers (*anti : syn* = 89.9 : 10.1, 34%) were obtained, both are colorless oil, the combined yield was 84% (222 mg). *anti*-**11**: $[\alpha]_D^{20}$ – 30.0° (*c* 1.13, $CHCl_3$). IR: 3066, 2989, 2955, 2850, 1743, 1456, 1437, 1373, 1273, 1191, 1177, 1095, 1018, 831, 768, 749, 667 cm^{-1}. ^{1}H-NMR (500Mz, $CDCl_3$), major *anti*-isomer: δ 1.16 (d, *J* = 7.11 Hz, 3H, C3-CH_3), 2.44 (s, 3H, SO_2Ph-CH_3-*p*), 3.09 (dq, *J* = 5.72, 7.11 Hz, 1H, H-3), 3.66 (s, 3H, $COOCH_3$), 3.72 (s, 3H, $COOCH_3$), 5.08 (d, *J* = 5.72 Hz, 1H, H-2), 7.36 (d, *J* = 8.20 Hz, 2H), 7.82 (d, *J* = 8.20 Hz, 2H) ppm. ^{13}C-NMR (125 Mz, $CDCl_3$) δ: 12.22 (Ph-CH_3), 21.69 (CH_3), 42.05 (C-3), 52.28 and 52.68 (COOMe), 78.15 (C-2), 128.17 and 129.71 (2×Ar–CH), 132.95 (Ar–CH), 145.21 (Ar-C), 167.69 and 171.29 (C=O)

ppm. MS (ESI): 683.4 ($2M^+$+23, 80), 354.1 (M^++23, 100). HRESIMS calcd for [$C_{14}H_{18}O_7S$+Na]$^+$: 353.0665; found: 353.0668. Anal. Calcd for $C_{14}H_{18}O_7S$: C, 50.9; H, 5.5; S, 9.7. Found: C, 51.1; H, 5.7; S, 9.4.

Dimethyl (2R, 3R)-2-methyl-3-phenylsultanylsuccinate (R-12)

Method 1: To a cooled (-10°C) solution of thiophenol (0.07 mL, 0.67 mmol) in anhydrous THF (0.7 mL) was added dropwise a solution of *n*-BuLi in hexane (2.5 M, 0.25 mL, 0.62 mmol), the mixture was stirred at rt for 0.5 h and then re-cooled to -10 °C. To this mixture was added a THF (0.5 mL) solution of **11** (170 mg, 0.52 mmol). After stirred at 0°C for 4 hours, a saturated $NaHCO_3$ solution (2 mL) was added. The reaction mixture was diluted with CH_2Cl_2 (10 mL), the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was washed with brine (1.5 mL) and dried with anhydrous Na_2SO_4. After flash chromatographic purification (eluent: EtOAc : PE = 1 : 10), isomers (**12** / **13**) were separated from **14**, the isomeric ratio was as follows: **12** : **13** : **14** = 36 : 24 : 40, the combined yield was 71%.

Method 2: To a ice-cooled solution of potassium thiophenolate (310 mg, 2.09 mmol) in absolute ethanol (1 mL) was added a solution of **11** (330 mg, 1.0 mmol) in absolute ethanol (0.5 mL). After stirred at rt for 4 h, a saturated NH_4Cl solution (2 mL) was added. After evaporation of ethanol at reduced pressure, to the mixture were added CH_2Cl_2 (15 mL) and water (2 mL). The resulting mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was washed successively with water (2 mL) and brine (2 mL) and then dried with anhydrous Na_2SO_4. After flash chromatographic purification (eluent: EtOAc: PE = 1 : 10), an inseparable mixture of regio-isomers of **12** / **13**, as well as **14** were obtained (ratio : 90 : 5 : 5), the combined yield was 84%.

Method 3: To a ice-cooled suspension of **11** (200 mg, 0.61 mmol) and potassium carbonate (200 mg, 1.4 mmol) in dry ether (6 mL) was added thiophenol (0.17 mL, 1.5 mmol). After stirred at 5°C for 30 h, the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc : PE = 1 : 10), an inseparable mixture of regio-isomers of **12** / **13**, as well as **14** were obtained (ratio: 90: 5: 5), the combined yield was 90%. *syn*-isomer (**12**): $[\alpha]_D^{20}$ +120° (*c* 0.96, $CHCl_3$, **12** : **13 =** 94.7 : 5.3). IR: 3059, 2989, 2952, 2881, 2845, 1734, 1583, 1456, 1436, 1377, 1261, 1216, 1154, 1066, 1024, 1002, 920, 855, 749, 692 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$) δ: 1.44 (d, *J* = 7.22 Hz, 3H, C3-CH_3), 2.89 (dq, *J* = 7.22, 10.38 Hz, 1H, H-3), 3.64 (s, 3H, $COOCH_3$), 3.67 (s, 3H, $COOCH_3$), 3.77 (d,

J = 10.38 Hz, 1H, H-2), 7.30-7.50 (m, 5H, -SPh) ppm. ^{13}C-NMR (125 Mz, $CDCl_3$) δ: 15.28 (CH_3), 40.71 (C-3), 52.10 and 52.32 (COOMe), 53.19 (C-2), 128.59 (Ar–CH), 128.81, 129.06 (2×Ar–CH), 133.76 (Ar–C), 171.32 and 174.96 (C=O) ppm. MS (ESI): 559 ($2M^+$+23, 100), 291 (M^++23, 64), 269 (M^++1, 53). HRESIMS calcd for $[C_{13}H_{16}SO_4 + Na]^+$: 291.0662; found: 291.0663. Regio-isomer (**13**): ^{1}H-NMR (500 Mz, $CDCl_3$) δ: 1.58 (s, 3H, C2-CH_3), 2.64 (d, *J* = 16.54 Hz, 1H, H-3), 3.07 (d, *J* = 16.54 Hz, 1H, H-3), 3.64 (s, 3H, $COOCH_3$), 3.66 (s, 3H, $COOCH_3$), 7.30~7.50 (m, 5H, -SPh) ppm. *anti*-isomer (**14**): $[\alpha]_D^{20}$ +25.4° (*c* 1.6, $CHCl_3$). ^{1}H-NMR (500 Mz, $CDCl_3$) δ: 1.25 (d, *J* = 6.92 Hz, 3H, C3-CH_3), 2.99 (dq, *J* = 6.92, 9.92 Hz, 1H, H-3), 3.68 (s, 3H, $COOCH_3$), 3.74 (s, 3H, $COOCH_3$), 3.88 (d, *J* = 9.92 Hz, 1H, H-2), 7.30-7.50 (m, 5H, -SPh).

Dimethyl (R)-methylsuccinate (R-16) *(prepared via (R-**12**), **Method A**)*

To an inseparable mixture of **12** and **13** (500 mg, 1.86 mmol, **12** : **13** = 94.7 : 5.3) in ethanol (2 mL), was added freshly prepared Raney Ni (200 mg in 2 mL of EtOH). After stirred at rt under an atmosphere of N_2 for 12 h, the mixture was filtered over celite. Flash chromatographic purification on silica gel (eluent: EtOAc : PE = 1 : 15) provided known *R*-**16** (289 mg, 97%). $[\alpha]_D^{20}$ +8.27° (*c* 1.29, EtOH), 80.2% ee deduced from *R*-**18**. {lit.,[10] for (*R*-**16**): $[\alpha]_D^{17.9}$ +9.98° (EtOH) }. IR: 2961, 2925, 2853, 1743, 1457, 1261, 1094, 1017, 799 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): 1.23 (d, *J* = 7.18 Hz, 3H, C2-CH_3), 2.42 (dd, *J* = 6.08, 16.54 Hz, 1H, H-3), 2.76 (dd, *J* = 8.11, 16.54 Hz, 1H, H-3), 2.93 (ddq, *J* = 6.08, 7.18, 8.11 Hz, 1H, H-2), 3.68 (s, 3H, $COOCH_3$), 3.72 (s, 3H, $COOCH_3$). MS (ESI): 343 ($2M^+$+23, 100), 161.7 (M^++1, 20).

(R)-2-Methyl-1,4-butanediol (17) *(prepared via (R-**12**), **Method A**)*

To a ice-cooled suspension of LAH (170 mg, 4.5 mmol) in anhydrous ether (1 mL) was added, under an atmosphere of N_2, a solution of **16** (180 mg, 1.12 mmol) in ether (0.5 mL). After stirred at rt for 6 h, the mixture was cooled with a ice-bath, then wet ether (4 mL), water (0.2 mL), a 10% solution of sodium hydroxide (0.4 mL) and again water (0.1 mL) were added successively. The mixture was allowed to reach rt, stirred for 30 min, and filtered through celite. After concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc) affording diol (*R*-**17**) (99 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ +10.0° (*c* 1.73, MeOH), 80.2% ee { lit.,[12a] for (*R*-**17**): $[\alpha]_D^{22}$ +14.4° (*c*2.0, MeOH); lit.,[6] $[\alpha]_D^{20}$ +9.42° (*c* 1.04, MeOH), 65% ee; $[\alpha]_D^{20}$ +13.9° (*c* 1.35, MeOH), 97% ee; lit.,[12b] *S*-**17**: $[\alpha]_D^{20}$ –14.4° (*c* 0.6, MeOH); lit.,[6] $[\alpha]_D^{20}$ –13.8° (*c* 1.24, MeOH), 96% ee}. IR: 3336, 2925, 2873,

1457, 1382, 1260, 1035, 798 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.92 (d, *J* = 6.99 Hz, 3H, C2-CH_3), 1.56 (m, 1H, H-3), 1.62 (m, 1H, H-3), 1.80 (m, 1H, H-2), 3.41 (dd, *J* = 7.53, 10.57 Hz, 1H, H-1), 3.51 (s, br, 2H, -OH), 3.55 (dd, *J* = 4.51, 10.57 Hz, 1H, H-1), 3.64 (m, 1H, H-4), 3.75 (m, 1H, H-4). MS (ESI): 330.7 ($3M^+$+ 18, 100). HRESIMS calcd for $[2C_5H_{12}O_2 + H]^+$: 209.1747; found: 209.1744.

(R)-2-Methyl-1,4-bis(benzoyloxy)butane (18)

To a mixture of diol (**17**) (52 mg, 0.50 mmol) and DMAP (cat.) in anhydrous CH_2Cl_2 (2.0 mL) were added successively pyridine (0.1 mL, 1.25 mmol) and benzoyl chloride (0.13 mL, 1.1 mmol) at 0°C. After stirred at rt for 6 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and water, the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was washed successively with water (1.5 mL), a saturated $NaHCO_3$ solution (1.5 mL) and brine (1.5 mL) and dried with anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the residue was flash chromatographied (eluent: EtOAc: PE = 1 : 20) to give *R*-**18** (140 mg, 90%) as a colorless oil. (*R*)-2-Methyl-1,4-bis(benzoyloxy)butane (**18**) prepared by different method were subjected to chiral HPLC analysis using a Chiralcel® OB column. The retention times (t_R) for *S*-**18** and *R*-**18** were 15.2 min and 19.5 min respectively (hexane : *i*-PrOH = 95 : 5). (*R*-**18**) prepared *via* **method A** showed 80.2% ee; $[\alpha]_D^{20}$ –6.49° (*c* 1.48, $CHCl_3$); *R*-**18** prepared *via* **method B** showed 84.7% ee; $[\alpha]_D^{20}$ –7.22° (*c* 1.21, $CHCl_3$){lit.,[11] for *R*-**18**: $[\alpha]_D^{20}$ -9.5° (*c* 2.0, $CHCl_3$); (*S*-**18**): $[\alpha]_D^{20}$ +9.4° (*c* 2.0, $CHCl_3$)}. IR: 3063,3034, 2963, 1717, 1602, 1584, 1451, 1390, 1314, 1271, 1176, 1110, 1070, 1026, 968, 709, 687, 675 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): 1.14 (d, *J* = 6.83 Hz, 3H, C2-CH_3), 1.76 (m, 1H, H-2), 2.03 (m, 1H, H-3), 2.22 (m, 1H, H-3), 4.27 (d, *J* = 6.05 Hz, 2H, H-1), 4.46 (m, 2H, H-4), 7.30-8.05 (m, 10H, PhCO). ^{13}C-NMR (125 Mz, $CDCl_3$) : 15.87 (CH_3), 30.15 (C-3), 32.43 (C-2), 62.92 (C-1), 69.35 (C-4), 128.33 (4×Ar–CH), 128.36, 129.15 and 130.21 (2×Ar–CH), 132.90 and 132.93 (Ar–C), 166,55 (2×C=O). MS (ESI): 646.8 ($2M^+$+23, 100), 335.3 (M^++23, 5); HRESIMS calcd for $[C_{19}H_{20}O_4+Na]^+$: 335.1254; found: 335.1248.

Dimethyl (2RS, 3R)-2-chloro-3-methylsuccinate (19)

A mixture of tosylate (**11**) (500 mg, 1.52 mmol), anhydrous lithium chloride (97 mg, 2.27 mmol) and dry DMF (1.5 mL) was stirred at 70°C and under an atmosphere of N_2 for 10 h. After chilled to rt, water (4.5 mL) was added and the mixture was extracted with ether (3×3 mL). The combined organic phase

was washed successively with water (1.5 mL) and brine (1.5 mL) and then dried with anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, **19** was obtained as an inseparable diastereomeric mixture (ratio, 53 : 47 calculated from ^{1}H-NMR spectrum; combined yield 76%) which was used in the next step.

Dimethyl (R)-methylsuccinate (R-16) *[prepared via (R-**19**), **Method B**]*

To a mixture of diastereomers (**19**) (110 mg, 0.57 mmol) and 10% Pd-C (15 mg) were added methanol (0.7 mL) and triethylamine (0.12 mL, 0.85 mmol). The mixture was stirred at rt under an atmosphere of H_2 for 12 h. The mixture was filtered over celite. Flash chromatographic purification on silica gel (eluent: EtOAc : PE = 1 : 15) provided known *R*-**16** (80 mg, yield, 89%, 84.7% ee as determined on **18**). $[\alpha]_D^{20}$ +8.71° (*c* 1.10, EtOH).

(R)-2-Methyl-1,4-butanediol (17) *[prepared via (R-**19**), **Method B**]*

(*R*)-2-Methyl-1,4-butanediol (**17)** was prepared from (*R*-**16**) (prepared *via* (*R*-**19**), **method B**) following the procedure described above. $[\alpha]_D^{20}$ +11.7° (*c* 1.92, MeOH), 84.7% ee

(R)-2-Methyl-1,4-bis(p-toluenesulphonyloxy)butane (6)

To a ice-cooled solution of *R*-**17** [104 mg, 1.0 mmol, prepared *via R*-**19**, **Method B**] and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (2 mL) were added successively pyridine (0.23 mL, 2.8 mmol) and a solution of *p*-TsCl (476 mg, 2.5 mmol) in anhydrous CH_2Cl_2 (2 mL). After stirred at 5°C for 10 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and water, the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was washed successively with water (1.5 mL), saturated $NaHCO_3$ solution (1.5 mL) and brine (1.5 mL) and dried with anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the residue was flash chromatographied (eluent: EtOAc : PE = 1 : 5) to give *R*-**6** [7] (352 mg, yield, 85%) as a pale yellow oil. $[\alpha]_D^{20}$ +0.92° (*c* 1.09, $CHCl_3$), 84.7% ee. IR: 3066, 2967, 2926, 1598, 1456, 1356, 1189, 1175, 1097, 1038, 940, 887, 836, 814, 784, 764 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.86 (d, *J* = 6.84 Hz, 3H, CH_3), 1.46 (m, 1H, H-3), 1.74 (m, 1H, H-3), 1.93 (m, 1H, H-2), 2.46 (s, 6H, $PhCH_3$), 3.79 (dd, *J* = 5.65, 9.63 Hz, 1H, H-1), 3.83 (dd, 1H, *J* = 5.43, 9.63 Hz, H-1), 4.01 (m, 2H, H-4) 7.35-7.76 (m, 8H, Ph-H) ppm. ^{13}C-NMR (125 Mz, $CDCl_3$): δ 15.87 (CH_3), 21.64 (2×CH_3), 29.40 (C-3), 31.73 (C-2), 67.81 (C-1), 73.95 (C-4), 127.83 and 129.89 (4×

Ar–CH), 132.72 and 132.78 (Ar-CH_3), 144.89 (2×Ar-SO_2) ppm. MS (ESI): 847.4 ($2M^+$+23, 100), 435.4 (M^++23, 10). HRESIMS calcd for $[C_{19}H_{24}O_6S_2+Na]^+$: 435.0907; found: 435.0908. Anal. Calcd for $C_{19}H_{24}O_6S_2$: C, 55.3; H, 5.8; S, 15.5. Found: C, 55.4; H, 6.1; S, 15.4.

(R)-3-Methyl-N-(3-methylbutyl)pyrrolidine [(R)-Leptothoracine] (1)

A mixture of *R*-**6** (240 mg, 0.58 mmol, prepared *via R*-**19**, **Method B**) and 3-methylbutylamine (0.36 mL, 3.1 mmol) was stirred at rt under an atmosphere of N_2 for four days. After diluted with ether (5 mL), filtered through celite, and concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel [eluent: ether / PE / ammonia = 1 : 1 : 0.01] affording **1**[4-7] (60 mg, 66%) as a colorless liquid. $[\alpha]_D^{20}$ –1.54° (*c* 0.95, EtOH), 84.7% ee [deduced from *R*-**18**]. {lit.,[6] for *R*-**1**: $[\alpha]_D^{20}$ –1.80° (*c* 0.96, EtOH); *S*-**1**: $[\alpha]_D^{20}$ +1.81° (*c* 3.03, EtOH), 96% ee}. IR: 2962, 2906, 1412, 1261, 1020, 865, 800, 700 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): 0.89 (d, *J* = 6.55 Hz, 6H, CH_3), 1.02 (d, *J* = 6.86 Hz, 3H, CH_3), 1.28-1.34 (m, 1H, H-4), 1.35-1.42 (m, 2H, H-2'), 1.58 (m, 1H, H-3'), 1.93-1.98 (m, 1H, H-2), 1.98-2.05 (m, 1H, H-4), 2.24 (m, 1H, H-3), 2.34- 2.46 (m, 3H, H-1', H-5), 2.68 (m, 1H, H-5), 2.83 (m, 1H, H-2). ^{13}C-NMR (125 Mz, $CDCl_3$): 20.22 (Me- (C-3)), 22.71 (Me_2CH), 26.69 (C-3'), 31.76 (C-3), 32.49 (C-4), 37.65 (C-2'), 54.18 (C-1'), 54.99 (C-5), 62.18 (C-2). MS (ESI): 156.5 (M^++ 1, 100). HRESIMS calcd for $[C_{10}H_{21}N+H]^+$: 156.1747; found: 156.1744.

(R)-3-Methyl-N-(2-phenylethyl)pyrrolidine (R-2)

A mixture of *R*-**6** [330 mg, 0.8 mmol, prepared *via R*-**19**, **Method B**] and 2-phenylethylamine (0.5 mL, 4.0 mmol) was stirred at rt under an atmosphere of N_2 for two days. After diluted with ether (3 mL), filtered through celite, and concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: ether / PE / ammonia = 1 : 1 : 0.01) affording *R*-**2** [4-7] (146 mg, yield, 96%) as a colorless liquid. $[\alpha]_D^{20}$ –1.87° (*c* 1.0, EtOH), 84.7% ee [deduced from *R*-**18**]. IR: 3062, 3026, 2954, 2926, 2870, 1785, 1605, 1497, 1453, 1159, 1128, 748, 698 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.04 (d, *J* = 6.77 Hz, 3H, CH_3), 1.36 (m, 1H, H-4), 2.00-2.09 (m, 2H, H-2, H-4), 2.27 (m, 1H, H-3), 2.49 (m, 1H, H-5), 2.60-2.84 (m, 5H, H-1', H-2', H-5), 2.90 (m, 1H, H-2), 7.10-7.30 (m, 5H, Ph). ^{13}C-NMR (125 Mz, $CDCl_3$): δ 20.29 (Me- (C-3)), 31.76 (C-3), 32.52 (C-4), 35.62 (C-2'), 54.15 (C-5), 58.51 (C-1'), 62.19 (C-2), 125.87 (C-5_p), 128.22 ($2C_m$), 128.53 ($2C_o$), 140.41 (C_{ipso}). MS (ESI): 190.5 (M^++1, 100); HRESIMS calcd for $[C_{13}H_{19}N+H]^+$: 190.1590; found: 190.1587.

***(3R, 2'S)-3-Methyl-N-(2-methylbutyl)pyrrolidine* (3)**

A mixture of *R*-**6** [168 mg, 0.41 mmol, prepared *via R*-**19**, **Method B**] and (*S*)-(-)-2-methylbutylamine (250 mg, 2.87 mmol) was stirred at rt under an atmosphere of N_2 for four days. After diluted with ether (4 mL), filtered through celite, and concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: ether / PE / ammonia = 1 : 1 : 0.01) affording **3** [4-6] (45 mg, 71%) as a colorless liquid. $[\alpha]_D^{20}$ +17.5° (*c* 0.94, EtOH), 84.7% ee [deduced from *R*-**18**]. IR (film) ν_{max}: 2959, 2925, 2873, 2786, 1454, 1376, 1260, 1176, 1097, 1020, 803 cm^{-1}. ^{1}H-NMR (500 Mz, $CDCl_3$): 0.88 (t, *J* = 7.37 Hz, 3H, CH_3), 0.91 (d, *J* = 6.61 Hz, 3H, CH_3), 1.01 (d, *J* = 6.91 Hz, 3H, CH_3), 1.10(m, 1H, H-3'), 1.33 (m, 1H, H-4), 1.40-1.54 (m, 2H, H-2', H-3'), 1.94-2.05 (m, 2H, H-2, H-4), 2.19-2.32 (m, 3H, H-3, H-1'), 2.38 (m, 1H, H-5), 2.70 (m, 1H, H-5), 2.82 (m, 1H, H-2). ^{13}C-NMR (125 Mz, $CDCl_3$): 11.37 ($MeCH_2$), 17.86 (MeCH), 20.28 (Me- (C-3)), 27.88 (C-3'), 31.87 (C-3), 32.46 (C-4), 33.77 (C-2'), 54.47 (C-5), 62.58 (C-2), 63.68 (C-1'). MS (ESI): 156.5 (M^++ 1, 100); HRESIMS calcd for [$C_{10}H_{21}N$+H]$^+$ 156.1747, found 156.1746.

ACKNOWLEDGMENTS

This work is supported by the National Science Fund for Distinguished Young Investigator (29625204), the NSF of China (29832020), the Visiting Scholar Foundation of Key Lab. In University, the Foundation for University Key Teacher by the Ministry of Education and Xiamen University. Pei-Qiang Huang dedicates this paper to the memory of his father.

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