Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3827–3832

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of (−)-(*R*)-pyrrolam A starting from (*S*)-malic acid

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Received 9 August 1999; accepted 31 August 1999

Abstract

An asymmetric synthesis of natural (−)-pyrrolam A starting from natural (*S*)-malic acid is described. The stereogenic center was established via a highly *trans*-diastereoselective reductive alkylation procedure. A tandem base-induced intramolecular amide *N*-substitution and tosic acid elimination led to the target molecule.

1. Introduction

More than 200 pyrrolizidine alkaloids have been isolated from plants and insects.[1] In 1990, four structurally related pyrrolizidinones, namely, pyrrolams A–D, were isolated from *Streptomyces olivaceus* (strain, TU3082).[2] Among them, pyrrolam A **1**, a structurally simple but biosynthetically new pyrrolizidinone, has attracted recent attention due both to its bioactivity[2] of causing damage to fertilized eggs at a low concentration and to the presence of a double bond, which is important to the hepatotoxic, mutagenic and carcinogenic activities of common pyrrolizidine alkaloids.[3] To date two asymmetric syntheses of natural enantiomer (−)-(*R*)-pyrrolam A **1**[4] and one asymmetric synthesis of ent-**1**[5] have been reported. However, the existing methods for (−)-(*R*)-pyrrolam A **1**, although efficient, need to use expensive unnatural D-proline as starting material.[4] Moreover, none of the known syntheses have been achieved via asymmetric induction. In continuation of our efforts to use cheap and easily available (*S*)-malic acid in the asymmetric synthesis of N-containing bioactive compounds,[6] we now report an asymmetric synthesis of natural enantiomer (−)-(*R*)-pyrrolam A **1**.

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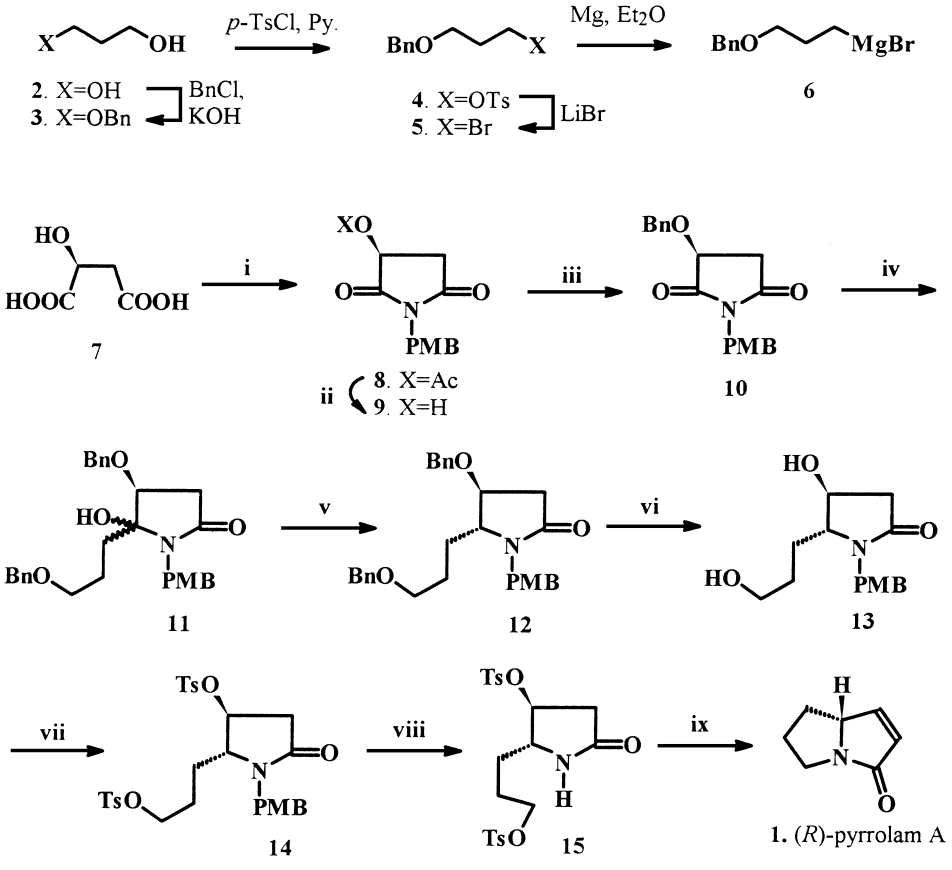
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00395-X

2. Results and discussion

The synthetic route is displayed in Scheme 1. The requisite C_3 unit **6** was prepared from 1,3-propanediol by successive monobenzylation,[7] tosylation,[7] bromination and Grignard reagent formation. On the other hand, natural (*S*)-malic acid was converted to the known (*S*)-malimide **8**[8] by a one-pot procedure.[6,8] Cleavage of the acetyl group under acidic conditions (AcCl, EtOH, 50°C) gave compound **9** (91% yield), which was protected as its benzyl ether **10** (94% yield).



Scheme 1. Reagents and conditions: (i) Louwrier et al.;[8] (ii) AcCl, EtOH, 50°C, 91%; (iii) BnBr, Ag_2O, Et_2O, room temperature, 94%; (iv) $BnO(CH_2)_3MgBr$, THF, 0°C, 90%; (v) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78°C to rt, 68%; (vi) H_2, 1 atm, 10% Pd/C, 95% EtOH, rt, 80%; (vii) *p*-TsCl, Py., cat. DMAP, CH_2Cl_2, 0°C to rt, 60%; (viii) CAN, MeCN:H_2O (3:1), 0°C, 77%; (ix) NaH, THF, −15–0°C, 83.5%

Reaction of an excess of 3-benzyloxy propyl magnesium bromide **6** to malimide **10** at 0°C led to a diastereomeric mixture (in ca. 50:50 ratio, combined yield 90%) of **11** in high regioselectivity which was deduced from the followed step. The high regioselectivity (>95%) of Grignard reagent addition to the more hindered carbonyl α to the C-3 benzyloxy group could be attributed to complex induced proximity effects (CIPE).[9] Presumably, the oxygen atom at C-3 chelates to magnesium to deliver the alkylmetal to the neighboring C-2 carbonyl group. One observation in support of this hypothesis is that the sodium borohydride reduction of **10** (at C-2 carbonyl group) to the γ-carbinol lactam completed in 15 min at −10°C, while the reduction of the C-3 unsubstituted *N*-benzyl malimide required several hours at room temperature. In addition, the explanation proposed by Speckamp[10] to account for the regioselective

reduction of *gem*-disubstituted succinimides can also be used to explain the observed regioselectivity. Such an explanation is based on both the observed complete coplanarity of the imide carbonyl groups and the general proposal for nucleophilic addition to carbonyl groups. Thus, the Grignard reagent approaches via the less hindered carbonyl group and adds to the carbon atom of the more hindered one along a straight line through the C–O bond.

The poor stereoselectivity observed in the Grignard reagent addition might reflect the overall results of the CIPE (*cis*-directing effect) and steric effects (*trans*-directing effect). The stereochemistry of the isomeric **11** was not assigned. This diastereomeric mixture, although separable by flash chromatography, was used in the next step as it was, since the following Lewis acid mediated ionic hydrogenation[11] was considered to proceed by the intermediacy of an *N*-acyliminium.[11a,b,12] Indeed, in the presence of 3.1 equivalents of boron trifluoride etherate, hydroxylactams **11** were reduced with excess of triethylsilane[11c] (CH_2Cl_2, −78°C to rt) to yield predominantly *trans*-**12** in 68% yield. The *trans*/*cis* diastereoselectivity was more than 95:5 according to chromatographic separation. The stereochemistry of compounds **12** was tentatively assigned to *trans* according to the observed vicinal coupling constants[6,13] ($J_{4,5}$=1.6 Hz). This was further confirmed by converting **12** to (−)-(*R*)-pyrrolam A **1**. The observed high regioselectivity in the Grignard addition to **10** and the high diastereoselectivity in the ionic hydrogenation of **11** were in agreement with our earlier results.[6] A chelation controlled model[6a] has been proposed to account for the observed high diastereoselectivity.

Catalytic hydrogenation (10% Pd/C, H_2, 1 atm) of **12** afforded diol **13** in a yield of 80%. Ditosylation of **13** led to **14** (60% yield) which, after oxidative *N*-deprotection using ceric ammonium nitrate in a mixed MeCN–H_2O solvent system, provided **15** in 77% yield. The remaining steps were the base-induced cyclization and tosic acid elimination. It was considered that these two steps could be accomplished in a single vessel. Indeed, treatment of a THF solution of **15** with an excess of sodium hydride at low temperature provided the desired (−)-(*R*)-pyrrolam A **1** {83.5% yield, mp 60.5°C, $[\alpha]_D^{20}$ −26.3 (*c* 0.4, $CHCl_3$) [lit.: mp 62°C, $[\alpha]_D^{20}$ −29.3 (*c* 1.0, $CHCl_3$);[2] mp 60–62°C, $[\alpha]_D^{20}$ −26.3 (*c* 0.31, $CHCl_3$);[4a] mp 59°C, $[\alpha]_D^{20}$ −26.3 (*c* 0.8, $CHCl_3$)[4b]]}. The physical data of the synthetic molecule were identical with those of the natural product.[2,4,5]

In summary, we have developed the first asymmetric synthesis of natural enantiomer (−)-(*R*)-pyrrolam A **1** from cheap and easily available natural (*S*)-malic acid.

3. Experimental

Melting points were determined on a Yanaco MP-500 micro melting point apparatus. Infrared spectra were measured with a Nicholet Avatar 360 FT-IR spectrometer using film NaCl or KBr pellet techniques. ^{1}H NMR spectra were recorded on either a Varian unity +500 or a Varian unity +360 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded on an HP 5988A apparatus or a Finnigan MAT-GCQ apparatus (direct injection). HRFABMS spectra were recorded on a Bruker APEX-II FTMS apparatus. MS spectra were presented as *m/z* (% rel. int.). Optical rotations were measured with a Perkin–Elmer 341 MC automatic polarimeter. Elemental analyses were performed by the Micro Analytical Laboratory at Shanghai Institute of Organic Chemistry. Tetrahydrofuran and diethyl ether used in the reactions were dried by distillation over metallic sodium and benzophenone; CH_2Cl_2 was distilled over CaH_2. Silica gel (Qingdao, 400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60–90°C) mixtures. (*S*)-4-Acetoxy-1-(4-methoxybenzyl)-2,5-pyrrolidinedione **8**[8] was prepared according to the literature procedure.

3.1. (S)-4-Hydroxy-1-(4-methoxybenzyl)-2,5-pyrrolidinedione **9**

To a solution of **8**[8] (4.217 g, 15.2 mmol) in 56 mL of absolute ethanol was added dropwise AcCl (3.2 mL, 45.0 mmol). The resulting mixture was stirred at 50°C for 5 h and concentrated in vacuo. Benzene was added, then concentrated in vacuo (this procedure was repeated three times). Flash chromatography (EtOAc:PE, 1:1.5) afforded **9** as a white solid (3.266 g, 91% yield). Mp 114.5–115.5°C (CH_2Cl_2), $[\alpha]_D^{20}$ −15.4 (*c* 0.52, $CHCl_3$). IR (KBr) ν_{max}: 3440, 1695, 1610, 1510, 1430, 1300, 1250, 1100 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.67 (dd, *J*=4.8, 18.0 Hz, 1H, H-4), 3.06 (dd, *J*=8.5, 18.0 Hz, 1H, H-4), 3.09 (s, 1H, OH), 3.79 (s, 3H, OCH_3), 4.61 (s+m, 3H, $PhCH_2$ and H-3), 6.84 (d, *J*=8.5 Hz, 2H, Ar-H), 7.33 (d, *J*=8.5 Hz, 2H, Ar-H). MS (EI): 235 (M^+, 93), 178 (20), 121 (100), 91 (9), 77 (18), 43 (15). Anal. calcd for $C_{12}H_{13}O_4N$: C, 61.26; H, 5.58; N, 5.96; found: C, 61.24; H, 5.37; N, 5.81.

3.2. (S)-4-Benzyloxy-1-(4-methoxybenzyl)-2,5-pyrrolidinone **10**

To a solution of **9** (549 mg, 2.34 mmol) in 20 mL of diethyl ether were added benzyl bromide (0.83 mL, 6.98 mmol) and silver oxide (1.95 g, 8.43 mmol). After stirring in the dark for 2 days at room temperature, the mixture was filtered through Celite and concentrated in vacuo. Flash chromatography (EtOAc:PE, 1:5 then 1:3) afforded **10** (714 mg, 94% yield) as a white solid. Mp 67.5–68.5°C (EtOAc:PE), $[\alpha]_D^{20}$ −70.8 (*c* 0.94, $CHCl_3$). IR (KBr) ν_{max}: 2900, 1710, 1615, 1520, 1440, 1400, 1340, 1305, 1255, 1180, 1035, 910, 840, 750, 710 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.66 (dd, *J*=4.2, 18.2 Hz, 1H, H-4), 2.94 (dd, *J*=8.0, 18.2 Hz, 1H, H-4), 3.79 (s, 3H, OCH_3), 4.35 (dd, *J*=4.2, 8.0 Hz, 1H, H-4), 4.59 (d, *J*=14.1 Hz, 1H, $PhCH_2N$), 4.63 (d, *J*=14.1 Hz, 1H, $PhCH_2N$), 4.79 (d, *J*=11.7 Hz, 1H, $PhCH_2O$), 4.99 (d, *J*=11.7 Hz, $PhCH_2O$), 6.92–7.38 (m, 9H, ArH). MS (EI): 325 (M^+, 2), 234 (2), 219 (17), 162 (11), 121 (100), 91 (31). Anal. calcd for $C_{19}H_{19}O_4N$: C, 76.07; H, 6.88; N, 3.41; found: C, 76.29; H, 6.65; N, 3.22.

3.3. (+)-(4S,5R)-4-Benzyloxy-5-(3′-benzyloxypropyl)-1-(4-methoxybenzyl)-2-pyrrolidinone **12**

A solution of **10** (2.302 g, 7.08 mmol) in anhydrous THF (28 mL) was cooled to 0°C under argon, and the Grignard reagent (24 mL, 1.5 mol L^{-1}, 36 mmol) in diethyl ether was added dropwise. After stirring at 0°C for 2 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (72 mL) and extracted with CH_2Cl_2 (3×45 mL). The combined extracts were washed with brine, dried with anhydrous $MgSO_4$ and concentrated in vacuo. Filtration through a short pad of column eluting with ethyl acetate:petroleum ether (60:40) yielded a mixture of two diastereomers **11** (3.042 g, 90%). The diastereomeric mixture was used as it was in the next step.

A mixture of the diastereomers obtained above (2.225 g, 4.7 mmol) was dissolved in dry CH_2Cl_2 (12 mL) under argon. The solution was cooled to −78°C, and triethylsilane (9.8 mL, 43.3 mmol) and trifluoroboron etherate (1.80 mL, 14.4 mmol) were added. After stirring at −78°C for 6 h, the reaction temperature was allowed to rise slowly to room temperature and quenched by a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude was flash chromatographed (EtOAc:PE, 1:1) to give *trans*-**12** (1.449 g, yield 68%) as colorless oils. $[\alpha]_D^{20}$ +19.9 (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 2940, 2860, 1685, 1610, 1510, 1450, 1245, 1095, 1025 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.40–1.90 (m, 4H, $2CH_2$), 2.52 (dd, *J*=2.0, 17.5 Hz 1H, H-3), 2.72 (dd, *J*=6.3, 17.5 Hz, 1H, H-3), 3.40 (t, *J*=6.0 Hz, 2H, $BnOCH_2$), 3.49 (ddd, *J*=1.6, 5.7, 8.8 Hz, 1H, H-5), 3.78 (s, 3H, OCH_3), 3.86 (ddd, *J*=6.3, 2.0, 1.6 Hz, 1H, H-4), 3.89 (d, *J*=15.2 Hz, 1H, NCH_2Ar), 4.38 (d, *J*=11.8 Hz, 1H, $PhCH_2OCH$), 4.43 (d, *J*=11.8 Hz, 1H, $PhCH_2OCH$), 4.45 (s, 2H, $PhCH_2OCH_2$), 4.98 (d, *J*=15.2 Hz, 1H, NCH_2Ar), 6.82, 7.14–7.36 (2m, 2H+12H, 2×H-aro).

MS (EI): 459 (M^+, 4), 368 (4), 351 (43), 340 (13), 279 (8), 260 (10), 230 (10), 217 (57), 121 (100), 91 (44). HRFABMS calcd for $[C_{29}H_{34}NO_4+H]^+$: 460.2482; found: 460.2475.

*3.4. (+)-(4S,5R)-4-Hydroxyl-5-(3′-hydroxypropyl)-1-(4-methoxybenzyl)-2-pyrrolidinone **13***

To a solution of **12** (1.414 g, 3.08 mmol) in 20 mL of 95% ethanol was added 10% Pd/C (375 mg). The mixture was hydrogenated under 1 atm hydrogen pressure and stirred at room temperature for 78 h. The mixture was filtered through Celite and the filtrate was evaporated in vacuo. Flash chromatography (EtOAc:MeOH, 25:1) afforded **13** (685 mg, 80%) as a pale yellow oil. $[\alpha]_D^{20}$ +31.0 (*c* 1.5, $CHCl_3$). IR (film) ν_{max}: 3375, 2930, 2860, 1650, 1615, 1510, 1440, 1245, 1030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.41 (m, 1H), 1.54 (m, 2H), 1.75 (m, 1H), 2.42 (d, br, *J*=17.2 Hz, 1H, H-3), 2.62 (s, 2H, 2OH), 2.83 (dd, *J*=6.0, 17.2 Hz, 1H, H-3), 3.35 (d, m, *J*=7.8 Hz, 1H, H-5), 3.61 (m, 2H, CH_2OH), 3.78 (s, 3H, OCH_3), 3.94 (d, *J*=15.0 Hz, 1H, CH_2Ar), 4.19 (d, br, *J*=6.0 Hz, 1H, H-4), 4.92 (d, *J*=15.0 Hz, CH_2Ar), 6.86 (d, *J*=8.6 Hz, 2H, C_6H_4), 7.19 (d, *J*=8.6 Hz, 2H, C_6H_4). MS (EI): 280 (M^++1, 8), 279 (M^+, 38), 261 (4), 217 (59), 167 (48), 149 (100), 121 (64). HRFABMS calcd for $[C_{15}H_{22}NO_4+H]^+$: 280.1543; found: 280.1540.

*3.5. (+)-(4S,5R)-1-(4-Methoxybenzyl)-4-(4-methylphenylsulfonyloxy)-5-[3′-(4-ethylbenzylsulfonyloxy)-propyl]-2-pyrrolidinone **14***

To an ice-bath cooled solution of **13** (624 mg, 2.24 mmol) in CH_2Cl_2 containing a catalytic amount of DMAP (32 mg) and dry pyridine (0.5 mL, 6.27 mmol) was added *p*-TsCl (1.09 g, 5.70 mmol). The mixture was stirred at room temperature for 76 h. The reaction was quenched with water (15 mL) and extracted with diethyl ether (3×5 mL). The combined extracts were washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (EtOAc:PE, 1:1) afforded **14** (794 mg, 60% yield) as a pale yellow oil. $[\alpha]_D^{20}$ +10.2 (*c* 2.2, $CHCl_3$). IR (film) ν_{max}: 2955, 2920, 1690, 1610, 1595, 1510, 1440, 1354, 1245, 1170, 1095, 900, 810, 660 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.20–1.72 (m, 4H, $2CH_2$), 2.41 (dd, *J*=1.8, 18.2 Hz, 1H, H-3), 2.45 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.66 (dd, *J*=6.7, 18.2 Hz, 1H, H-3). 3.48 (ddd, *J*=1.7, 3.3, 9.1 Hz, 1H, H-5), 3.81 (s, 3H, OCH_3), 3.85 (d, *J*=15.0 Hz, 1H, NCH_2), 3.91 (t, *J*=5.9 Hz, 2H, $TsOCH_2$), 4.72 (ddd, *J*=1.7, 1.8, 6.7 Hz, 1H, H-4), 4.85 (d, *J*=15.0 Hz, 1H, NCH_2Ar), 6.83 (d, *J*=8.6 Hz, 2H, C_6H_4), 7.09 (d, *J*=8.6 Hz, 2H, C_6H_4), 7.32 (d, *J*=8.0 Hz, 2H, $C_6H_4SO_2$), 7.35 (d, *J*=8.0 Hz, 2H, $C_6H_4SO_2$), 7.66 (d, *J*=8.2 Hz, 2H, $C_6H_4SO_2$), 7.76 (d, 8.2 Hz, 2H, $C_6H_4SO_2$). HRFABMS calcd for $[C_{29}H_{34}NO_8S_4+H]^+$: 588.1720; Found: 588.1711.

*3.6. (+)-(4S,5R)-4-(4-Methylbenzylsulfonyloxy)-5-[3′-(4-methylphenylsulfonyloxy)propyl)]-2-pyrrolidinone **15***

To a solution of compound **14** (636 mg, 1.08 mmol) dissolved in a mixed MeCN:H_2O solvent system (3:1, 4 mL) was added, at 0°C, ceric ammonium nitrate (2.368 g, 4.32 mmol). After stirring at the same temperature for 20 min, glacial H_2O (15 mL) was added. The resulting mixture was extracted with ethyl acetate (4×5 mL). The combined extracts were washed with a saturated aqueous sodium bicarbonate, dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (EtOAc:PE, 2:1) afforded **15** (388 mg, 77% yield) as a white crystal. Mp 159–160°C, $[\alpha]_D^{20}$ +5.2 (*c* 0.9, $CHCl_3$). IR (KBr) ν_{max}: 3450, 1707, 1370, 1355, 1187, 1170, 950, 656 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$): 1.60–1.80 (m, 4H, $2CH_2$), 2.31 (dd, *J*=3.0, 18.1 Hz, 1H, H-3), 2.46 (s, 3H, $ArCH_3$), 2.47 (s, 3H, $ArCH_3$), 2.58 (dd, *J*=7.0, 18.1 Hz, H-3), 3.69 (m, 1H, H-5), 4.01 (t, *J*=5.5 Hz, 2H, $TsOCH_2$), 4.74 (ddd, *J*=3.0, 3.0, 7.0 Hz,

1H, H-4), 6.09 (s, 1H, NH), 7.38, 7.78 (2m, each 4H, H-aro). HRFABMS calcd for $[C_{21}H_{25}NO_7S_2+H]^+$: 468.1145; found: 468.1149.

*3.7. (−)-(R)-1-Azabicyclo[3.3.0]oct-3-ene-2-one (Pyrrolam A) **1***

A solution of **15** (50 mg, 0.11 mmol) in anhydrous THF (18 mL) was cooled to −10°C under argon, and a suspension of NaH (14 mg, 0.58 mmol) in anhydrous THF (7 mL) was added dropwise. After stirring at the same temperature for 1 h, then at 0°C for 2.5 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (8 mL) and extracted with dichloromethane (4×15 mL). The combined extracts were washed with brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. Filtration through a short pad of column (SiO_2, $CHCl_3$:MeOH, 90:10) yielded a crude which was further purified by HPLC (using $CHCl_3$ as eluent) to give (*R*)-**1** (11 mg, 83.5%) as a colorless solid. Mp 61.5°C, $[\alpha]_D^{20}$ −26.3 (*c* 0.4, $CHCl_3$) [lit.: mp 62°C, $[\alpha]_D^{20}$ −29.3 (*c* 1.0, $CHCl_3$);[2] mp 60–62°C, $[\alpha]_D^{20}$ −26.3 (*c* 0.31, $CHCl_3$);[4a] mp 59°C, $[\alpha]_D^{20}$ −26.3 (*c* 0.8, $CHCl_3$)[4b] for natural (*R*)-**1**; mp 60°C, $[\alpha]_D^{20}$ +25.7 (*c* 1, $CHCl_3$)[5] for unnatural (*S*)-**1**]. IR (KBr) ν_{max}: 3083, 2972, 2891, 1675, 1374, 1326, 1245, 1096, 811 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): 1.19 (m, 1H), 2.20 (m, 1H), 2.30–2.45 (m, 2H), 3.20–3.45 (m, 2H), 4.42 (m, 1H, H-5), 6.05 (dd, *J*=1.5, 5.7 Hz, 1H, H-3), 7.45 (dd, 1H, *J*=1.6, 5.7 Hz, H-4). MS (EI): 124 (M^++1, 22), 123 (M^+, 66), 95 (61), 94 (78), 67 (100), 59 (61). HRFABMS calcd for $[C_7H_9NO+H]^+$: 124.0757; found: 124.0758.

Acknowledgements

This work is supported by the National Science Fund for Distinguished Young Investigator under grant No. 29 625 204. The National NSF of China (grant No. 29572065) is thanked for additional support.

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