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Tetrahedron 62 (2006) 12334–12339
Tetrahedron

Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols

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Received 8 September 2006; revised 29 September 2006; accepted 2 October 2006
Available online 27 October 2006

Abstract—Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols has been established starting from 2-benzyloxymethylpyrrolidin-2-one framework, which is derived from commercially available *trans*-(2*S*,4*R*)-4-hydroxyproline. The single diastereomer having a trans–cis relative configuration with C_2 and C_3 and C_3 and C_4 is constructed in two one-pot functional group transformations of Grignard addition/dehydration and epoxidation/isomerization as the key steps in moderate yield.

1. Introduction

Based on the structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline, it possesses three functional groups that can be easily modified and they are 1-amino, 2-carboxylate and 4-hydroxy groups.[1] The skeleton represents the significant feature for producing a series of different carbon frameworks such as monocycles (pyrrole,[2a] pyrrolidine,[2b,c,l] piperidine[2d] and azanucleoside[2e]), fused or bridged bicycles (pyrrolizidine[2f] or azabicycles[2g,h,m]), polycycles,[2i–k,n] macrocycle,[2o] etc. using an efficient modification technique.

Recently, we have introduced a facile and straightforward approach toward monocyclic pyrrolidine (anisomycin)[2l] and piperidine (α-conhydrine),[2m] bicyclic bridged 7-azabicyclo[2.2.1]heptane (epibatidine)[2n] and pyrrolophane (streptorubin B core),[2o] bicyclic fused hexahydro-1*H*-indol-3-one (pancracine)[2p] and acyclic γ-amino acid (statin and vigabatrin®)[2q,r] skeleton system via some easy functional group transformations, intramolecular basic alkylation, acidic aldol condensation, ring-closing metathesis and regioselective Baeyer–Villiger oxidation of different 2-substituted pyrrolidin-4-one framework employing *trans*-(2*S*,4*R*)-4-hydroxyproline as the starting material.

To demonstrate the synthetic utility of our methodology and explore the application to the synthesis of 2-substituted pyrrolidin-4-one, synthetic studies toward (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols were investigated (Fig. 1). Our interest in synthesizing 4-aryl-3-hydroxyprolinol (4-aryl-3-hydroxy-2-hydroxymethylpyrrolidine) skeleton was piqued on the different biological properties and because it is with the motif of 3-hydroxyl group and is a key intermediate for preparing many important skeletons of substituted piperidines and prolines.[3] Prolinol is an α-aminoalcohol with a unique nature inducing specific electronic and geometric features. The presence of such a ring in the chemical structure restricts conformational flexibility, which may efficiently modify binding affinity to its target. In addition, this peptidomimetic compound is expected to be more stable to hydrolysis by metabolic enzymes.

(2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinol *trans*-(2*S*,4*R*)-4-hydroxyproline

Figure 1. Structures of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinol and *trans*-(2*S*,4*R*)-4-hydroxyproline.

2. Results and discussion

2.1. Retrosynthetic analysis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols 1a–d

We now wish to report an easy and straightforward synthesis of (2*S*)-2-benzyloxymethylpyrrolidin-4-one **3** leading to four (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d** by two remarkable one-pot transformations as shown in Scheme 1. One

Keywords: (2*R*,3*S*,4*S*)-4-Aryl-3-hydroxyprolinols; *trans*-(2*S*,4*R*)-4-Hydroxyproline; One-pot reaction; Grignard addition/dehydration; Epoxidation/isomerization.
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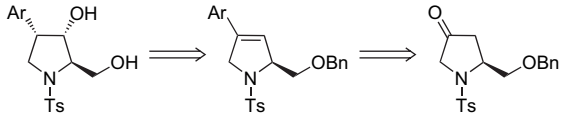
doi:10.1016/j.tet.2006.10.002

is the access to produce (2*S*)-4-aryl-2-benzyloxymethyl-2,5-dihydropyrroles **2a–d** by the Grignard addition of compound **3** and subsequent boron trifluoride etherate mediated dehydration of the resulting tertiary alcohols. The other is a specific step from olefins **2a–d** to diols **1a–d** by stereochemical epoxidation and followed by boron trifluoride etherate mediated isomerization of the resulting epoxides.

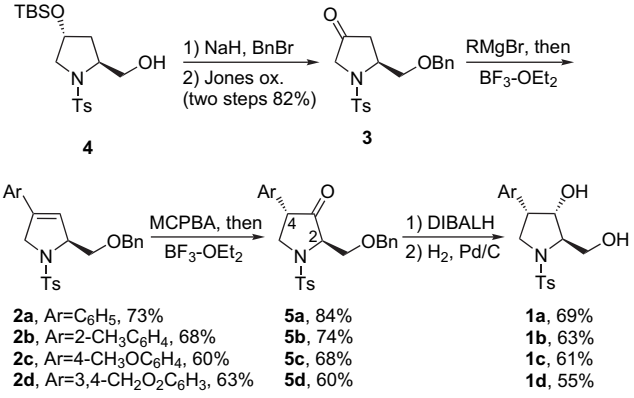


a, Ar=C_6H_5; **b**, Ar=2-$CH_3C_6H_4$; **c**, Ar=2-$CH_3OC_6H_4$; **d**, Ar=3,4-$CH_2O_2C_6H_3$

Scheme 1. Retrosynthetic analysis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d**.

2.2. Synthesis of (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols 1a–d

In a previous report,[2m–q] synthesis of prolinol **4** from *trans*-(2*S*,4*R*)-4-hydroxyproline provided a 90% overall yield with purification done only once via a facile four-step reaction. As shown in Scheme 2, prolinol **4** was first transformed into ketone **3** (82% yield in two steps) by *O*-benzylation and Jones oxidation under the standard conditions. With enough amounts of ketone **3**, conversion of ketone **3** into olefins **2a–d** was further examined.



Scheme 2. Synthetic approach toward (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d**.

Treatment of ketone **3** with different arylmagnesium bromide reagents (a, Ar=C_6H_5; b, Ar=2-$CH_3C_6H_4$; c, Ar=4-$CH_3OC_6H_4$; d, Ar=3,4-$CH_2O_2C_6H_3$) in tetrahydrofuran provided a pair of diastereoisomers (ca. 1:1 ratio) without any induction onto the stereoselectivity.[4a] Following this similar approach, attempts to form a sole tertiary alcohol under a variety of conditions (prolonged reaction time, diverse temperature, different solvents) were unsuccessful.[4]

With these results in hand, the direct one-pot conversion for the reaction of ketone **3** with four arylmagnesium bromide reagents and subsequent dehydration of the resulting tertiary alcohols with boron trifluoride etherate yielded compounds **2a–d** in 60–73% overall yield. During the one-pot process, 4-aryl-2-benzyloxymethyl-2,3-dihydropyrrole framework was not observed. In the other way, one-pot reaction of ketone **3** with methylmagnesium bromide and followed by dehydration was also examined. Treatment of 4-hydroxy-4-methyl-2-benzyloxymethylpyrrolidine yielded 4-methyl-2-benzyloxymethyl-2,5-dihydropyrrole in trace amounts under the acidic conditions (e.g., boron trifluoride etherate, aluminum chloride and Dean–Stark distillation). Based on these results, we envisioned that aryl group is an important substituent, which easily provides a stable benzylic cation in the dehydration process. However, 4-methyl-2-benzyloxymethyl-2,5-dihydropyrrole was carried out in 34% yield by the basic dehydration of this tertiary alcohol with mesyl chloride and pyridine.

To investigate the relative stereochemistry of diols **1a–d** at C_2 and C_3 and C_3 and C_4 positions, epoxidation of olefins **2a–d** and isomerization of the resulting epoxides **2aa–da** were studied in the next stage. Epoxidation of model substrate **2a** with *m*-chloroperoxybenzoic acid afforded a sole epoxide **2aa** with three contiguous asymmetric centers in 92% yield. The structural stereochemistry of epoxide **2aa** was determined by single-crystal X-ray analysis (Diagram 1).[5] According to the provided epoxide **2aa**, we envisioned that stereoselective epoxidation of olefin **2a** was strongly affected by the steric hindrance of 2-benzyloxymethyl group.[6] Both 4-phenyl and 2-benzyloxymethyl groups in the structure of epoxide **2aa** could be arranged as *cis* configuration. Next, ketone **5a** was afforded by the selective isomerization of trisubstituted epoxide **2aa** via hydride shift in 91% yield.[7] Therefore, the stereochemical assignment of ketone **5a** at C_2 and C_4 centers was made the trans configuration.

For the epoxidation of olefins **2c–d** with electron-donating groups, the desired epoxides **2ca–da** could not be obtained and complex products were isolated during silica gel chromatography. With the previous experiences in mind,[8] we envisioned that the problem was solved by the one-pot reaction. Therefore, ketones **5a–d** were yielded via the one-pot reaction of olefins **2a–d** with the combination of *m*-chloroperoxybenzoic acid and followed by boron trifluoride etherate in 60–84% overall yield. Ketones **5a–d** must be purified by recrystallization from dichloromethane and methanol because the generated racemic mixture was observed by the epimerization of C_2 or C_4 position during silica gel-mediated chromatographic purification.

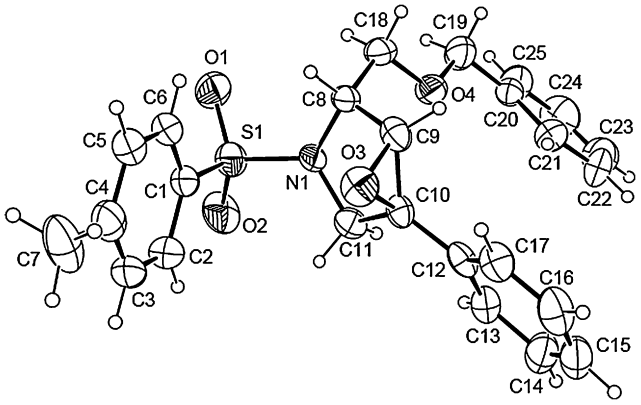


Diagram 1. X-ray crystallography of epoxide **2aa**.

Briefly, ketones **5a–d** were obtained via the stereoselective epoxidation of olefins **2a–d** with *m*-chloroperoxybenzoic acid and followed by isomerization of the resulting epoxides **2aa–da** with boron trifluoride etherate. Two one-pot procedures of Grignard addition/dehydration and epoxidation/isomerization were monitored by TLC until the reaction was completed. The overall simple procedure was achieved within one working day.

With the requisite ketones **5a–d** in hand, we examined the reduction of ketones **5a–d**. When the model substrate **5a** was treated with sodium borohydride or lithium aluminum hydride under different temperatures, two diastereoisomers were obtained in a 2:3 ratio. Therefore, reduction of ketone **5a** with diisobutylaluminum hydride at −78 °C afforded the sole benzyl alcohol **5aa**. Other benzyl alcohols **5ba–da** were also afforded by this reduction. Finally, hydrogenolysis of the benzyl alcohols **5aa–da** with a catalytic amount of 10% palladium on activated carbon yielded (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d**. According to the literature reports,[9] the coupling constant (J_{H3-H4} value) with cis configuration was approximately determined to be about 2.8–4.2 Hz in the prolinol or proline skeleton.[3f,9c,h] In comparison with the prolinols **1a–d**, we believe that the relative stereochemical centers at C_3 and C_4 positions were also assigned by correlation of the H_3–H_4 coupling constant (e.g., **1a**, δ 4.45, J_{H3-H4}=4.0 Hz). Thus, the assignment of three contiguous stereocenters on pyrrolidine framework of compounds **1a–d** was made the trans–cis configuration.

3. Conclusion

In summary, we have developed two one-pot Grignard addition/dehydration and epoxidation/isomerization as the key transformations for synthesizing (2*R*,3*S*,4*S*)-4-aryl-3-hydroxyprolinols **1a–d** with potential biological activities. Further application of this methodology to the synthesis of 4-methyl-3-hydroxyproline (4-HMP), which is the common constituent of the active echinocandin family,[10] is now underway.

4. Experimental

4.1. General

Tetrahydrofuran was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo.

4.2. (2*S*)-2-Benzyloxymethyl-1-(4-methylphenylsulfonyl)pyrrolidin-4-one (3)

A solution of prolinol **4** (7.7 g, 20.0 mmol) in tetrahydrofuran (100 mL) was added to a rapidly stirred suspension of sodium hydride (1.60 g, 60%, 40.0 mmol) in tetrahydrofuran (30 mL). After the reaction mixture was stirred at room temperature for 20 min, a solution of benzyl bromide (5.0 g, 29.0 mmol) in tetrahydrofuran (100 mL) was added. The reaction mixture was stirred at refluxed temperature for 20 h. The resulting mixture was cooled to room temperature, quenched with aqueous ammonium chloride solution (15%, 10 mL) and concentrated. The residue was extracted with ethyl acetate (3×150 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product. Without further purification, excess Jones reagent (15 mL) was added to a stirred solution of resulting benzyl compound in acetone (200 mL) at 0 °C. The mixture was stirred for 20 min and treated with 2-propanol (10 mL) to destroy the unreacted oxidizing reagent. After the solvent was removed, the residue was diluted with water (10 mL) and extracted with diethyl ether (3×150 mL). The combined organic layers were dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate=4:1) afforded compound **3** (5.9 g, two steps 82%). White solid; mp=118–119 °C; $[\alpha]_D^{25}$ +41.10 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 2959, 1766, 1312, 1141, 1094, 688 cm^{-1}; FAB-MS: $C_{19}H_{22}NO_4S$ *m*/*z* (%)=91 (100), 155 (19), 224 (36), 238 (52), 360 (M^++1, 17); HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1272; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.5 Hz, 2H), 7.32–7.26 (m, 5H), 7.16 (d, *J*=8.5 Hz, 2H), 4.43 (d, *J*=12.0 Hz, 1H), 4.43–4.38 (m, 1H), 4.37 (d, *J*=12.0 Hz, 1H), 3.78 (dd, *J*=3.5, 9.5 Hz, 1H), 3.76 (s, 2H), 3.52 (dd, *J*=3.5, 9.5 Hz, 1H), 2.43 (s, 3H), 2.39–2.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.09, 144.08, 137.39, 135.36, 130.01 (2×), 128.41 (2×), 127.75, 127.31 (2×), 127.07 (2×), 73.37, 73.22, 56.84, 53.92, 40.47, 21.52; Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.41; H, 6.01; N, 3.71.

4.3. A representative procedure with one-pot reaction for the preparation of olefins 2a–d

A solution of different arylmagnesium bromide reagents (1.0 M in tetrahydrofuran, 1 mL, 1.0 mmol) was added to a stirred solution of ketone **3** (180 mg, 0.5 mmol) in tetrahydrofuran (20 mL) at −78 °C. The reaction mixture was stirred at room temperature for 2 h. The total procedure was monitored by TLC until the reaction was completed. Without further purification, boron trifluoride etherate (1 mL) was added to a stirred solution of the resulting reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. Water (2 mL) and ethyl acetate (10 mL) were added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure to yield the crude compound. Purification on silica gel (hexane/ethyl acetate=8:1–4:1) afforded olefins **2a–d** in 60–73% overall yield.

4.3.1. 2-Benzyloxymethyl-4-phenyl-1-(4-methylphenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (2a). Viscous oil; $[\alpha]_D^{24}$ −12.45 (*c* 0.043, $CHCl_3$); IR ($CHCl_3$) 2360, 1636, 1345, 1163, 1092, 754, 695 cm^{-1}; FAB-MS: $C_{25}H_{26}NO_3S$ *m*/*z* (%)=91 (100), 137 (28), 154 (20), 298 (6), 420 (M^++1, 15); HRMS (ESI, M^++1) calcd for $C_{25}H_{26}NO_3S$ 420.1633,

found 420.1632; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J=8.5 Hz, 2H), 7.36–7.26 (m, 12H), 6.14 (br d, J=2.0 Hz, 1H), 4.70–4.65 (m, 1H), 4.62–4.54 (m, 1H), 4.59 (s, 2H), 4.43 (d, J=14.0 Hz, 1H), 4.03 (dd, J=4.0, 9.5 Hz, 1H), 3.63 (t, J=9.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.71, 138.13, 137.15, 134.06, 132.35, 129.84 (2×), 128.64 (2×), 128.48, 128.40 (2×), 127.70 (2×), 127.68, 127.50 (2×), 125.52 (2×), 122.14, 73.96, 73.67, 67.13, 55.80, 21.50. Anal. Calcd for $C_{25}H_{25}NO_3S$: C, 71.57; H, 6.01; N, 3.34. Found: C, 71.68; H, 6.29; N, 3.57.

4.3.2. 2-Benzyloxymethyl-4-(2-methylphenyl)-1-(4-methylphenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (2b). Viscous oil; $[\alpha]_D^{26}$ −12.20 (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 2359, 1634, 1160, 668 cm^{-1}; HRMS (ESI, M$^+$+1) calcd for $C_{26}H_{28}NO_3S$ 434.1790, found 434.1791; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.5 Hz, 2H), 7.36–7.28 (m, 7H), 7.20–7.12 (m, 3H), 7.00 (d, J=7.5 Hz, 1H), 5.75 (dd, J=2.0, 4.0 Hz, 1H), 4.76–4.73 (m, 1H), 4.61 (d, J=12.0 Hz, 1H), 4.58 (d, J=12.0 Hz, 1H), 4.44 (ddd, J=2.0, 5.0, 14.5 Hz, 1H), 4.36 (dt, J=2.0, 14.5 Hz, 1H), 3.97 (dd, J=3.5, 9.0 Hz, 1H), 3.68 (dd, J=7.0, 9.0 Hz, 1H), 2.42 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.67, 138.17, 138.08, 135.90, 134.26, 132.98, 130.82, 129.77 (2×), 128.37 (2×), 127.99, 127.87, 127.63 (3×), 127.51 (2×), 125.93, 125.81, 73.81, 73.59, 67.46, 57.92, 21.51, 20.88. Anal. Calcd for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28; N, 3.23. Found: C, 72.19; H, 6.12; N, 3.44.

4.3.3. 2-Benzyloxymethyl-4-(4-methoxyphenyl)-1-(4-methylphenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (2c). Viscous oil; $[\alpha]_D^{26}$ +61.67 (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 2922, 2358, 1652, 1515, 1344, 1162, 1094, 817, 590 cm^{-1}; HRMS (ESI, M$^+$+1) calcd for $C_{26}H_{28}NO_4S$ 450.1739, found 450.1740; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=8.5 Hz, 2H), 7.38–7.27 (m, 7H), 7.22 (d, J=9.0 Hz, 2H), 6.85 (d, J=9.0 Hz, 2H), 6.00 (br d, J=2.0 Hz, 1H), 4.66–4.64 (m, 1H), 4.59 (s, 2H), 4.54 (ddd, J=2.0, 5.0, 13.5 Hz, 1H), 4.40 (dt, J=2.0, 13.5 Hz, 1H), 4.02 (dd, J=4.0, 9.0 Hz, 1H), 3.80 (s, 3H), 3.62 (t, J=8.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.72, 143.63, 138.17, 136.55, 134.08, 129.80 (2×), 128.37 (2×), 127.68 (2×), 127.64, 127.48 (2×), 126.81 (2×), 125.08, 119.90, 113.98 (2×), 74.07, 73.64, 67.09, 55.89, 55.29, 21.48. Anal. Calcd for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12. Found: C, 69.61; H, 5.83; N, 3.35.

4.3.4. 2-Benzyloxymethyl-4-(3,4-dioxymethylenephenyl)-1-(4-methylphenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (2d). Viscous oil; $[\alpha]_D^{26}$ −38.32 (*c* 0.007, $CHCl_3$); IR ($CHCl_3$) 2360, 1635, 1558, 668 cm^{-1}; HRMS (ESI, M$^+$+1) calcd for $C_{26}H_{26}NO_5S$ 464.1532, found 464.1535; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=8.5 Hz, 2H), 7.38–7.27 (m, 7H), 6.81 (d, J=1.5 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H), 6.70 (dd, J=1.5, 8.0 Hz, 1H), 5.97 (d, J=2.0 Hz, 1H), 5.95 (s, 2H), 4.66–4.61 (m, 1H), 4.59 (s, 2H), 4.50 (ddd, J=2.0, 5.0, 14.0 Hz, 1H), 4.37 (d, J=14.0 Hz, 1H), 4.01 (dd, J=4.0, 9.0 Hz, 1H), 3.63 (t, J=8.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.00, 147.83, 143.69, 138.14, 136.68, 134.07, 129.83 (2×), 128.40 (2×), 127.70 (2×), 127.68, 127.50 (2×), 126.67, 120.65, 119.47, 108.23, 105.77, 101.25, 73.96, 73.65, 67.02, 55.93, 21.51. Anal. Calcd for $C_{26}H_{25}NO_5S$: C, 67.37; H, 5.44; N, 3.02. Found: C, 67.50; H, 5.70; N, 3.21.

4.4. A general representative procedure with one-pot reaction for the preparation of ketones 5a–d

m-Chloroperoxybenzoic acid (70 mg, 75%, 0.3 mmol) was added to a solution of olefins **2a–d** (0.2 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 3–5 h. The total procedure was monitored by TLC until the reaction was completed. Without further purification, boron trifluoride etherate (1 mL) was added to a stirred solution of the resulting epoxides **2aa–da** at 0 °C. The reaction mixture was stirred at room temperature for 15 min. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude products under reduced pressure. Recrystallization from dichloromethane and methanol yielded the ketones **5a–d**. Besides ketone **5a**, it is worthy of note that ketones **5b–d** are slow in producing some epimers under the deuterated chloroform condition.

4.4.1. 4-Benzyloxymethyl-3-(4-methylphenylsulfonyl)-1-phenyl-6-oxa-3-aza-bicyclo[3.1.0]hexane (2aa). White solid; mp=115–116 °C; $[\alpha]_D^{28}$ +27.48 (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) 2925, 2358, 1634, 1453, 1342, 1163, 1096, 814 cm^{-1}; FAB-MS: $C_{25}H_{26}NO_4S$ *m/z* (%)=91 (100), 298 (20), 328 (15), 436 (M$^+$+1, 13); HRMS (ESI, M$^+$+1) calcd for $C_{25}H_{26}NO_4S$ 436.1582, found 436.1584; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J=8.0 Hz, 2H), 7.32–7.27 (m, 10H), 7.18 (dd, J=2.0, 8.0 Hz, 2H), 4.58 (d, J=11.5 Hz, 1H), 4.52 (d, J=11.5 Hz, 1H), 4.12 (t, J=4.0 Hz, 1H), 4.03 (d, J=12.5 Hz, 1H), 3.86 (d, J=4.0 Hz, 2H), 3.78 (d, J=12.5 Hz, 1H), 3.60 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.54, 137.75, 135.36, 133.21, 129.60 (2×), 128.53, 128.47 (2×), 128.39 (2×), 127.78, 127.70 (2×), 127.53 (2×), 126.05 (2×), 73.74, 71.19, 65.99, 65.49, 61.10, 51.35, 21.60. Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 69.03; H, 5.92; N, 3.51. Single-crystal X-ray diagram: crystal of epoxide **2aa** was grown by slow diffusion of ethyl acetate into a solution of compound **2aa** in dichloromethane to yield colorless prism. The compound crystallizes in the monoclinic crystal system. a=7.778(16) Å, b=16.074(3) Å, c=18.523(4) Å, V=2315.7(8) Å^3, Z=4, d_{calcd}=1.249 mg/m^3, absorption coefficient 0.170 mm^{-1}, $F(000)$=920, 2θ range (2.20–25.99°), wR_2=0.1304.

4.4.2. 2-Benzyloxymethyl-4-phenyl-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (5a). White solid; mp=124–125 °C; $[\alpha]_D^{27}$ −4.05 (*c* 0.037, $CHCl_3$); IR ($CHCl_3$) 2358, 1764, 1348, 1165, 1091, 815, 662, 549 cm^{-1}; FAB-MS: $C_{25}H_{26}NO_4S$ *m/z* (%)=91 (100), 155 (11), 314 (29), 328 (10), 341 (15), 436 (M$^+$+1, 11); HRMS (ESI, M$^+$+1) calcd for $C_{25}H_{26}NO_4S$ 436.1582, found 436.1584; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=8.0 Hz, 2H), 7.36–7.23 (m, 10H), 7.03 (dd, J=2.0, 8.0 Hz, 2H), 4.52 (d, J=12.0 Hz, 1H), 4.47 (d, J=12.0 Hz, 1H), 4.23 (dd, J=9.0, 9.5 Hz, 1H), 4.09 (dd, J=2.5, 10.0 Hz, 1H), 3.94

(dd, J=2.0, 10.0 Hz, 1H), 3.81 (dd, J=9.0, 9.5 Hz, 1H), 3.77 (dd, J=2.0, 2.5 Hz, 1H), 3.52 (dd, J=9.0, 9.5 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.44, 144.26, 137.66, 134.54, 133.54, 129.93 (2×), 128.91 (2×), 128.36 (2×), 128.05 (2×), 127.78, 127.70 (2×), 127.69, 127.44 (2×), 73.66, 70.24, 64.70, 53.37, 51.60, 21.57. Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22. Found: C, 68.61; H, 5.89; N, 3.57.

4.4.3. 2-Benzyloxymethyl-4-(2-methylphenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (5b). Viscous oil; $[\alpha]_D^{27}$ −2.31 (c 0.01, $CHCl_3$); IR ($CHCl_3$) 2360, 1771, 1346, 1159, 1088, 760 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{26}H_{28}NO_4S$ 450.1739, found 450.1743; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J=8.1 Hz, 2H), 7.32–7.25 (m, 7H), 7.20–7.13 (m, 3H), 6.99 (d, J=7.2 Hz, 1H), 4.50 (d, J=10.8 Hz, 1H), 4.44 (d, J=10.8 Hz, 1H), 4.27 (dd, J=9.0, 9.6 Hz, 1H), 4.06 (dd, J=2.4, 10.2 Hz, 1H), 3.96 (dd, J=2.4, 10.2 Hz, 1H), 3.85 (dd, J=9.0, 9.6 Hz, 1H), 3.80 (dd, J=2.4, 2.7 Hz, 1H), 3.50 (dd, J=9.0, 9.6 Hz, 1H), 2.45 (s, 3H), 2.15 (s, 3H); Anal. Calcd for $C_{26}H_{27}NO_4S$: C, 69.46; H, 6.05; N, 3.12. Found: C, 69.87; H, 6.39; N, 3.43.

4.4.4. 2-Benzyloxymethyl-4-(4-methoxyphenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (5c). Viscous oil; $[\alpha]_D^{29}$ −12.53 (c 0.006, $CHCl_3$); IR ($CHCl_3$) 2355, 1761, 1345, 1162, 1090, 766 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{26}H_{28}NO_5S$ 466.1688, found 466.1689; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=8.1 Hz, 2H), 7.39–7.18 (m, 7H), 6.85 (d, J=9.0 Hz, 2H), 6.63 (d, J=9.0 Hz, 2H), 4.50 (d, J=10.8 Hz, 1H), 4.43 (d, J=10.8 Hz, 1H), 4.22 (dd, J=9.0, 9.6 Hz, 1H), 4.08 (dd, J=2.4, 10.2 Hz, 1H), 3.94 (dd, J=2.4, 10.2 Hz, 1H), 3.79 (s, 3H), 3.80–3.76 (m, 2H), 3.27 (dd, J=9.0, 9.6 Hz, 1H), 2.46 (s, 3H). Anal. Calcd for $C_{26}H_{27}NO_5S$: C, 67.08; H, 5.85; N, 3.01. Found: C, 66.83; H, 5.60; N, 2.84.

4.4.5. 2-Benzyloxymethyl-4-(3,4-dioxymethylenephenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (5d). Viscous oil; $[\alpha]_D^{29}$ −16.32 (c 0.008, $CHCl_3$); IR ($CHCl_3$) 2356, 1760, 1350, 1160, 1095 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{26}H_{26}NO_6S$ 480.1481, found 480.1481; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=8.1 Hz, 2H), 7.39–7.25 (m, 5H), 7.20–7.16 (m, 2H), 6.78 (d, J=8.1 Hz, 1H), 6.52 (d, J=1.2 Hz, 1H), 6.43 (dd, J=1.2, 8.1 Hz, 1H), 5.96 (s, 2H), 4.38 (d, J=10.8 Hz, 1H), 4.36 (d, J=10.8 Hz, 1H), 4.18 (dd, J=9.0, 9.6 Hz, 1H), 4.03 (dd, J=2.4, 10.2 Hz, 1H), 3.96 (dd, J=2.4, 10.2 Hz, 1H), 3.76 (dd, J=9.0, 9.6 Hz, 1H), 3.75 (dd, J=1.8, 2.4 Hz, 1H), 3.22 (dd, J=9.0, 9.6 Hz, 1H), 2.42 (s, 3H).

4.5. A representative procedure for the preparation of diols 1a–d

A solution of diisobutylaluminum hydride (1.0 M in hexane, 0.3 mmol) was added to a solution of ketones **5a–d** (0.1 mmol) in tetrahydrofuran (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h. The total procedure was monitored by TLC until the reaction was completed. Methanol (0.5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude benzyl alcohols **5aa–da** under reduced pressure. Palladium (10%) on activated carbon (30 mg) was added to a stirred solution of the resulting benzyl alcohols **5aa–da** in methanol (10 mL). Hydrogen was bubbled into the mixture for 10 min and stirring of the reaction mixture was continued for 10 h at room temperature. The catalyst was filtered through a short plug of Celite and washed with methanol (2×20 mL). The combined organic layers were evaporated to afford crude products. Purification on silica gel (hexane/ethyl acetate=2:1–1:1) afforded diols **1a–d**.

4.5.1. 2-Hydroxymethyl-4-phenyl-1-(4-methylphenylsulfonyl)pyrrolidin-3-ol (1a). White solid; mp=158–159 °C; $[\alpha]_D^{28}$ +23.82 (c 0.019, $CHCl_3$); IR ($CHCl_3$) 3430, 2358, 1634, 1339, 1160, 1089, 663 cm^{-1}; FAB-MS: $C_{18}H_{22}NO_4S$ m/z (%)=91 (100), 136 (13), 154 (10), 316 (30), 341 (5), 348 (M^++1, 7); HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_4S$ 348.1269, found 348.1267; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J=8.0 Hz, 2H), 7.37–7.26 (m, 5H), 7.13 (d, J=8.5 Hz, 2H), 4.45 (t, J=4.0 Hz, 1H), 4.14 (dd, J=5.5, 12.0 Hz, 1H), 4.11 (dd, J=4.0, 12.0 Hz, 1H), 3.92 (dd, J=11.5, 12.0 Hz, 1H), 3.88 (dd, J=8.0, 11.5 Hz, 1H), 3.76 (dd, J=4.0, 10.0 Hz, 1H), 2.66 (ddd, J=4.0, 8.0, 12.0 Hz, 1H), 2.46 (s, 3H), 1.68 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.08, 134.74, 134.17, 130.01 (2×), 128.79 (2×), 128.27 (2×), 127.65, 127.53 (2×), 75.68, 65.57, 62.63, 51.07, 48.65, 21.58. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.50; H, 6.23; N, 4.30.

4.5.2. C3 isomer of compound 1a. Viscous oil; $[\alpha]_D^{28}$ +10.68 (c 0.009, $CHCl_3$); IR ($CHCl_3$) 3432, 2916, 2849, 1636, 1159, 543 cm^{-1}; FAB-MS: $C_{18}H_{22}NO_4S$ m/z (%)=91 (100), 136 (18), 154 (16), 316 (26), 341 (8), 348 (M^++1, 6); HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_4S$ 348.1269, found 348.1268; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.30–7.23 (m, 3H), 7.07 (d, J=8.5 Hz, 2H), 4.18 (dd, J=5.0, 12.0 Hz, 1H), 4.04 (dd, J=8.0, 9.5 Hz, 1H), 3.98 (dd, J=3.0, 12.0 Hz, 1H), 3.88 (dd, J=8.0, 10.0 Hz, 1H), 3.75 (ddd, J=4.5, 5.0, 8.0 Hz, 1H), 3.39 (dd, J=9.5, 10.0 Hz, 1H), 3.05 (dd, J=10.0, 10.0 Hz, 1H), 2.48 (s, 3H), 2.10 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.19, 137.49, 132.94, 129.95 (2×), 128.86 (2×), 127.72 (2×), 127.57, 127.37 (2×), 77.55, 62.73, 61.33, 51.70, 49.98, 21.60. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.42; H, 5.83; N, 4.32.

4.5.3. 2-Hydroxymethyl-4-(2-methylphenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-ol (1b). White solid; mp=167–168 °C; $[\alpha]_D^{27}$ +16.67 (c 0.009, $CHCl_3$); IR ($CHCl_3$) 3428, 2920, 1635, 1338, 1160, 1091, 661, 545 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_4S$ 362.1426, found 362.1427; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=8.0 Hz, 2H), 7.37 (d, J=8.0 Hz, 2H), 7.19–7.14 (m, 4H), 4.40 (br s, 1H), 4.11 (br s, 2H), 3.97 (t, J=12.0 Hz, 1H), 3.87 (dd, J=5.0, 10.5 Hz, 1H), 3.76 (dd, J=7.0, 12.0 Hz, 1H), 2.78 (br s, 1H), 2.72–2.67 (m, 1H), 2.46 (s, 3H), 2.03 (br s, 1H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.07, 136.52, 134.40, 132.27, 130.84, 129.95 (2×), 127.62, 127.58 (2×), 127.48, 126.21,

73.49, 65.70, 62.66, 50.82, 45.19, 21.53, 19.36. Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.38; H, 6.80; N, 3.61.

4.5.4. 2-Hydroxymethyl-4-(4-methoxyphenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-ol (1c). Viscous oil; $[\alpha]_D^{26}$ +25.57 (*c* 0.009, $CHCl_3$); IR ($CHCl_3$) 3455, 2920, 1611, 1515, 1340, 1160, 1033, 817 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_5S$ 378.1375, found 378.1377; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 7.05 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 4.38 (br s, 1H), 4.11 (br s, 2H), 3.89–3.80 (m, 2H), 3.78 (s, 3H), 3.76–3.73 (m, 1H), 2.94 (br s, 1H), 2.64–2.59 (m, 1H), 2.46 (s, 3H), 2.42 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.01, 144.03, 134.19, 129.98 (2×), 129.31 (2×), 127.53 (2×), 126.43, 114.21 (2×), 75.65, 65.56, 62.63, 55.28, 51.28, 47.92, 21.57. Anal. Calcd for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71. Found: C, 60.22; H, 6.29; N, 3.90.

4.5.5. 2-Hydroxymethyl-4-(3,4-dioxymethylenephenyl)-1-(4-methylphenylsulfonyl)pyrrolidin-3-ol (1d, rotamer). Viscous oil; $[\alpha]_D^{26}$ +10.39 (*c* 0.008, $CHCl_3$); IR ($CHCl_3$) 3445, 2933, 1504, 1338, 1160, 1037, 663 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_6S$ 392.1168, found 392.1171; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.4 Hz, 2H), 7.39 (d, *J*=8.4 Hz, 2H), 6.77 (d, *J*=8.1 Hz, 1H), 6.63 (br s, 1H), 6.52 (dd, *J*=1.2, 8.1 Hz, 1H), 5.97 (s, 2H), 4.39 (br s, 1H), 4.16 (br s, 2H), 3.97–3.93 (m, 1H), 3.85–3.80 (m, 2H), 3.73–3.69 (m, 1H), 2.83 (br s, 1H), 2.66–2.62 (m, 1H), 2.45 (s, 3H).

Acknowledgements

The authors would like to thank the National Science Council (NSC-95-2113-M-390-003-MY2) of the Republic of China for financial support. We also thank Prof. Michael Y. Chiang (National Sun Yat-Sen University) for structural determination of epoxide **2aa** by X-ray diffraction analysis.

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