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ASYMMETRIC FORMAL SYNTHESIS OF (–)-FORMOTEROL AND (–)-TAMSULOSIN

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Abstract – Biologically important (2*R*)-2-amino-3-phenylpropanes consisted in commercial drugs including (*R*,*R*)-formoterol, and (*R*)-tamsulosin were prepared from chiral (2*R*)-aziridine-2-carboxylate without any chromatographic separation. Key reactions include regio- and stereoselective ring opening reaction of aziridin-2-yl-phenylmethanol and subsequent cyclization toward enantiopure 4,5-disubastitued oxazolidin-2-ones as synthetic intermediates.

Synthesis of amine-containing chiral drugs is always an important subject not only for the industrial interest but for the biological evaluation of each enantiomers.[1] Recently asymmetric synthesis of formoterol, β2-adrenoreceptor agonist to treat asthma and other bronchospastic conditions, attracts attention to find out the most active stereoisomer that was identified to be *R* of both stereocenters.[2] Its synthesis can achieve at ease from (2*R*)-2-amino-3-(4-methoxyphenyl)propane (**1**) and chiral epoxide.[3] Similar compound (2*R*)-2-amino-3-(4-methoxy-3-amidosulfonylphenyl)propane (**2**) consists in tamsulosin, commercial drug for the treatment of benign prostatic hyperplasia by acting on prostatic A1 adrenoceptors.[4] Syntheses of (*R*,*R*)-formoterol and (*R*)-tamsulosin were known to be achieved from chiral amines **1** and **2** respectively by the known methods.[3,5] Few methods were reported in the literature obtaining either **1** or **2** in optically pure form. These include separation of enantiomers or diastereomer with semipreparative HPLC and enzymatic resolution with limitation to get large scale of products in both cases.[6] Reductive amination of aldehyde with chiral amine is one good way to proceed, but diasteromeric ratio was very poor with less than 50%.

Both of those two compounds (**1** and **2**) are able to be elaborated from 4-methyloxazolidin-2-ones by reductive hydrogenation that would be formed from vicinal amino alcohol.

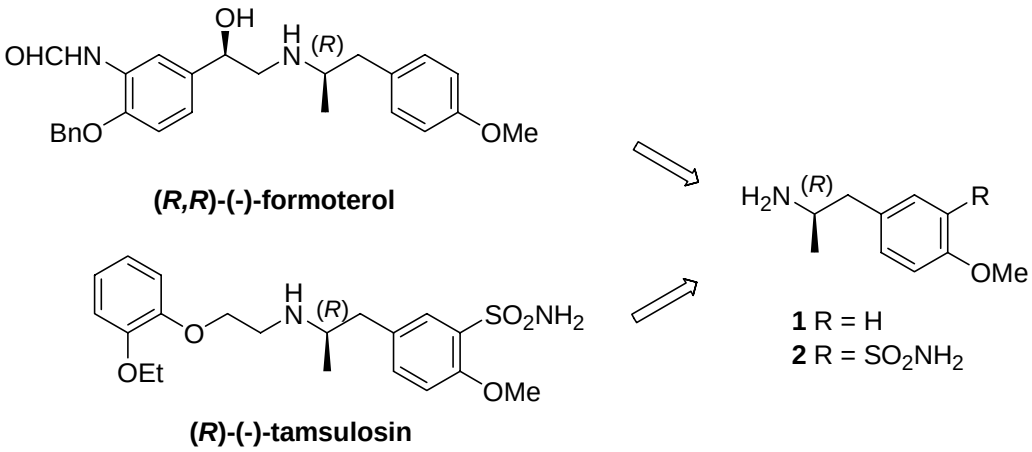
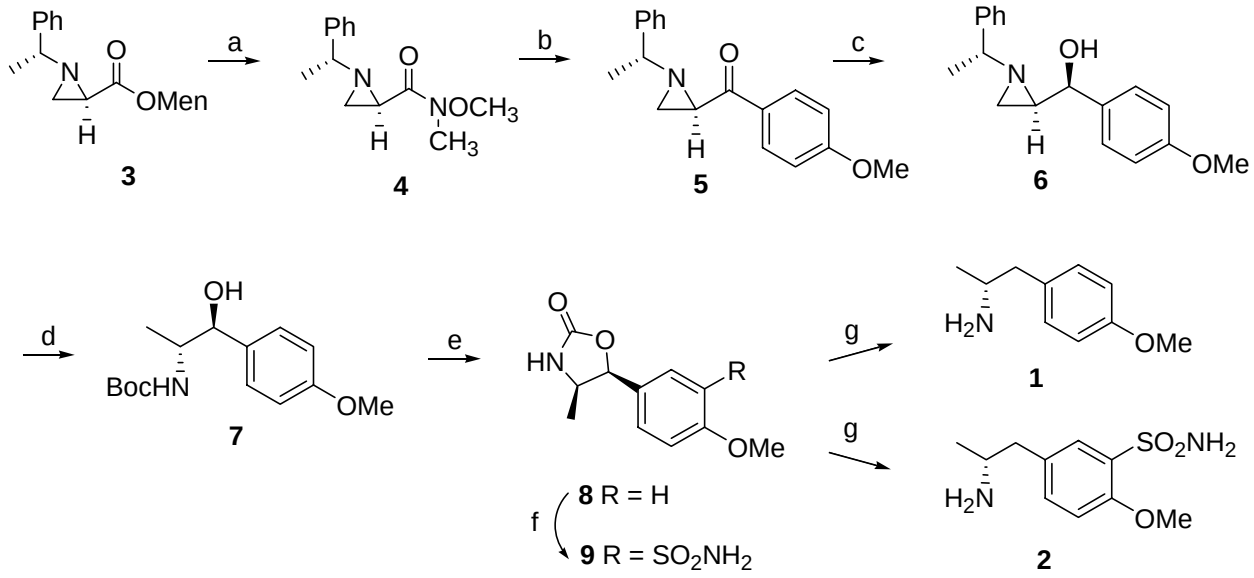


Figure 1

The possible common synthetic intermediates (4*R*)-4-methyl-5-phenyloxazolidin-2-one will be derived from regio- and stereoselective ring opening product of aziridin-2-yl-phenylmethanol originated from commercial (-)-menthyl aziridine-2-carboxylate in optically pure form. In this report is described an efficient asymmetric formal synthesis of commercial drugs formoterol and tamsulosin in gram-scale without chromatograph.

The main theme of this synthesis involves an efficient preparation of the synthetic intermediate (4*R*)-4-methyl-5-(4-methoxyphenyl)oxazolidin-2-one (**8**), from which (4*R*)-5-(4-methoxy-3-sulfamoylphenyl)-4-methyloxazolidin-2-one (**9**) is derived. First of all commercial (2*R*)-aziridine-2-carboxylate (**3**)[7] was treated with Weinreb'a amine whose product **4** was isolated and purified by crystallization from *n*-hexane in 89% yield. Addition of 4-methoxyphenylmagnesium bromide was followed to yield an acylaziridine (**5**). Reduction of acylaziridine[8] with $NaBH_4$ afforded **6** which was isolated as crystalline solid from *n*-hexane in 86% yield for two steps. Aziridin-2-yl-phenylmethanol (**6**) was hydrogenated in the presence of di-*t*-butyl dicarbonate ($(Boc)_2O$) to produce acyclic aminopropanol **7** in 89% yield (Scheme 1). Aminopropanol (**7**) with *t*-butoxycarbonyl (Boc) as an amine protecting group was treated with sodium hydride to give cyclized product **8** that was isolated as a crystalline solid form in 78% yield. This was reacted with chlorosulfonic acid in slow addition controlling the temperature not to be higher than 10ºC followed by addition of ammonia to give **9**. Both compounds **8** and **9** were treated with either hydrogen gas or ammonium formate in the presence of palladium on carbon to yield **1** and **2** respectively in more than 87% yields.[9]



Scheme 1. (a) MeNHOMe, *i*-PrMgCl, THF, 0ºC; (b) 4-$MeOC_6H_4MgBr$; (c) $NaBH_4$, $ZnCl_2$, MeOH; (d) $Pd(OH)_2$, H_2 (1 atm), Boc_2O, MeOH, rt; (e) NaH, THF, rt; (f) (i) $ClSO_3H$, (ii) NH_3; (g) HCO_2NH_4 or H_2 (1 atm), Pd•C, MeOH.

In summary biologically important (2*R*)-2-amino-3-phenylpropanes consisted in commercially drugs including (*R*,*R*)-formoterol, and (*R*)-tamsulosin were prepared from chiral (2*R*)-aziridine-2-carboxylate without any chromatographic separation. Key reactions include regio- and stereoselective ring opening reaction of aziridin-2-yl-phenylmethanol and subsequent cyclization toward enantiopure 4,5-disubstituted oxazolidin-2-ones followed by hydrogenation.

EXPERIMENTAL

General methods. ^{1}H NMR and ^{13}C-NMR spectra were recorded on a Varian 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C). Chemical shifts were given in ppm using TMS as an internal standard. Mass spectra were obtained using a Hewlett Packard Model 5985B spectrometer or a Kratos Concept 1-S double focusing mass spectrometer. Elemental analysis was taken on a Perkin-Elmer 240 DS elemental analyzer. Melting point was measured by Mel-II capillary melting point apparatus. Optical rotations were measured on Rudolph Research Autopole 3 polarimeter. Thin layer chromatography was carried out with Merck 60F-254 plates with 0.25 mm thickness. Starting chiral (-)-menthyl (2*R*,1'*R*)-(1'-phenylethyl)aziridine-2-carboxylate was purchased from Aldrich®.

(2*R*,1'*R*)-(1'-Phenylethyl)aziridine-2-carboxylic acid methoxymethylamide (4).[8] Into the solution of (-)-menthyl (2*R*,1'*R*)-(1'-phenylethyl)aziridine-2-carboxylate (**3**, 45 g, 0.136 mol) in THF (500 mL) was added methoxymethylamine (19.8 g, 0.20 mol) at 0 ºC. Then 200 mL of *iso*-propylmagnesium chloride solution (2 M in THF, 0.40 mol) was added slowly at 0 ºC. This solution was stirred for 0.5 h at 0 ºC before quenching the reaction by adding saturated aqueous NH_4Cl (60 mL). The mixture was extracted with EtOAc (500 mL) and water (100mL). The combined organic extracts were washed with water twice (300

mL x 2), dried by anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give white viscous liquid. This crude product was dissolved in *n*-hexane (80 mL) and the solution was cooled down to -10 ºC to afford white solid product (28.5g) in 89% yield. mp 67-68 ºC. $[\alpha]_D^{22}$ 33.6 (c 0.8, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (d, *J* = 6.8 *Hz*, 3H), 1.50 – 1.57 (m, 1H), 2.10 – 2.16 (m, 1H), 2.54 – 2.65 (m, 2H), 3.12 (s, 3H), 3.74 (s, 3H), 7.18 – 7.34 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 23.3, 32.6, 33.5, 35.8, 61.8, 69.9, 126.9, 127.3, 128.3, 143.7, 170.3.

(2*R*,1'*R*)-2-(1'-Phenylethyl)aziridinyl 4-methoxyphenyl ketone (5). (2*R*,1'*R*)-(1'-Phenylethyl)-aziridine-2-carboxylic acid methoxymethylamide (**4**, 24 g, 102 mmol) was dissolved in THF (270 mL) and the solution was cooled down to –10 ºC. Into this was added 4-methoxyphenylmagnesium bromide (240 mL of 0.5 M in THF, 120 mmol) slowly for 1 h. The resultant solution was stirred for 0.5 h at 0 ºC before adding 10 mL of water. The resultant solution was concentrated under reduced pressure and the residue was dissolved in 500 mL EtOAc. The organic layer was washed with water twice (300 mL x 2), dried by anhydrous $MgSO_4$ and concentrated with the removal of all solvent. This crude product in liquid was used for the next reaction without further purification. For the analysis we have obtained the product as a crystalline solid by recrystallization from *n*-hexane in 95% yield. mp 68-70 ºC. $[\alpha]_D^{22}$ 24.2 (c 2.1, EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (d, *J* = 6.6 *Hz*, 3H), 1.55 (dd, *J* = 6.6, 1.3 *Hz*, 1H), 2.05 – 2.08 (m, 1H), 2.49 (q, *J* = 6.6 *Hz*, 1H), 2.53 – 2.82 (m, 1H), 3.69 (s, 3H), 6.96 (d, *J* = 6.8 *Hz*, 2H), 7.21 – 7.33 (m, 5H), 8.14 (d, *J* = 6.8 *Hz*, 2H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 23.5, 33.6, 41.7, 55.6, 70.3, 114.0, 127.1, 127.4, 128.5, 130.0, 130.8, 143.8, 163.8, 194.6. IR: ν 2969, 1663, 1602, 1241, 1174, 1024 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{19}NO_2$: 281.1416, found: 281.1421.

(2*R*,1'*S*,1''*R*)-(1''-Phenylethyl)aziridine-2-yl-[1'-(4-methoxyphenyl)]methanol (6). (2*R*,1'*R*)-2-(1'-Phenylethyl)aziridinyl 4-methoxyphenyl ketone (**5**, 16.5 g, 58.6 mmol) was dissolved in MeOH (200 mL) and cooled down to -78 ºC. Into this solution was added $ZnCl_2$ (9.6 g, 70 mmol) and $NaBH_4$ (3.3 g, 88 mmol). The resultant solution was stirred for 0.5 h before adding 10 mL of water. The resultant solution was concentrated under reduced pressure and the residue was dissolved in 300 mL EtOAc. The organic layer was washed with water twice (150 mL x 2), dried by anhydrous $MgSO_4$ and concentrated with the removal of all solvent. This crude product in liquid was dissolved in *n*-hexane (20 mL) and kept at 0 ºC for 20 h. The crystalline products (13.2 g) was filtered and dried. In the mother liquor lots of products was left which was combined together with the next batch of the reaction to isolate the products. In most case we have obtained the products in 86% yield for two steps. mp 88-89 ºC. $[\alpha]_D^{22}$ = 25.2 (c 1.7, EtOAc). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 – 1.29 (m, 4H), 1.78 – 1.91 (m, 2H), 2.53 (q, *J* = 6.7 *Hz*, 1H), 3.04 (br s, 1H), 3.68 (s, 3H), 4.73 (s, 1H), 6.78 – 6.83 (m, 2H), 7.13 – 7.26 (m, 7H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 23.5, 19.8, 45.0, 55.3, 68.9, 71.2, 113.8, 123.9, 127.2, 127.7, 128.5, 134.5, 144.3, 159.2. IR: ν 3209, 2971, 1611, 1511, 1241, 1180, 1029 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{21}NO_2$: 283.1572, found: 283.1579.

(1*S*,2*R*)-2-[*N*-(*t*-Butoxycarbonyl)amino]-1-(4-methoxyphenyl)propanol (7). (2*R*,1'*S*,1''*R*)-(1''-Phenylethyl)aziridine-2-yl-[1'-(4-methoxyphenyl)]methanol (**6**, 13.0 g, 45.8 mmol) and di-*t*-butyl dicarbonate (10 g, 45.8 mmol) were dissolved in EtOH (92 mL). Into this solution was added $Pd(OH)_2$ (2.6 g) and the resultant solution was stirred for 8 h under atmospheric pressure of H_2 at rt. The solution was filtered and concentrated under *in vacuo* to yield crude product. Purification was carried out by crystallization from *n*-hexane (13 mL) to yield 11.5 g solid product in 89% yield. mp 132-133 ºC. $[\alpha]_D^{22}$ 4.8

(c 0.7, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (d, *J* = 7.0 *Hz*, 3H), 1.42 (s, 9H), 3.41 (brs, 1H), 3.77 (s, 3H), 3.91 (brs, 1H), 4.73 – 4.81 (m, 2H), 6.81 – 6.89 (m, 2H), 7.19 – 7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 14.7, 28.4, 52.0, 55.3, 76.2, 79.7, 113.5, 127.5, 133.3, 156.3, 158.0. IR: ν 3383, 2989, 1667, 1519, 1245, 1162, 1025 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{23}NO_4$: 281.1627, found: 281.1632.

(4*R*,5*S*)-5-(4-Methoxyphenyl)-4-methyloxazolidin-2-one (8). To the solution of (1*S*, 2*R*)-2-[*N*-(*t*-butoxycarbonyl)amino]-1-(4-methoxyphenyl)propanol (**7**, 11.3 g, 40 mmol) in THF (130 mL) was added NaH (1.2 g, 50 mmol). The resultant solution was stirred for 24 h before adding 5 mL of water. Then this solution was concentrated under reduced pressure. The mixture was extracted with EtOAc twice (100 mL x 2). The combined organic extracts were washed successively with water (100 mL) and saturated aqueous $NaHCO_3$ (100 mL), dried by anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. This crude product in liquid was dissolved in *n*-hexane (7 mL) and kept at 0 ºC for 20 h. The crystalline products (6.5 g) was filtered and dried. Yield 78%. mp 141-143 ºC. $[\alpha]_D^{22}$ 40.2 (c 1.6, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (d, *J* = 4.8 *Hz*, 3H), 3.96 (s, 3H), 4.17 – 4.25 (m, 1H), 5.69 (d, *J* = 7.6 *Hz*, 1H), 6.23 (brs, 1H), 6.87 – 9.85 (m, 2H), 7.21 – 7.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 17.5, 52.6, 55.3, 81.0, 113.9, 127.0, 127.4, 159.7, 160.0. IR: ν 3314, 2972, 1753, 1615, 1297, 1177, 1029 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{13}NO_3$: 207.0895, found: 207.0885.

(4*R*,5*S*)-5-(4-Methoxy-3-sulfamoylphenyl)-4-methyloxazolidin-2-one (9). To the solution of (1*S*, 2*R*)-5-(4-methoxyphenyl)-4-methyloxazolidin-2-one (**8**, 1.5 g, 7.2 mmol) was added slowly chlorosulfonic acid (26.3 mg, 225 mmol) at 0 ºC. This solution was stirred for 0.5 h at 0 ºC before addition of 10 mL ice water. The reaction product was extracted with EtOAc (50 mL x 2). The organic layer was washed successively with water (30 mL) and saturated aqueous $NaHCO_3$ (30 mL), dried by anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The concentrated organic material was dissolved in 20 mL THF that was bubbled by anhydrous ammonia gas until all starting material was gone. This crude product was concentrated again under reduced pressure and crystallized from *n*-hexane (3 mL). The crystalline products (1.94 g) was filtered and dried. Yield 94%. mp 228-230 ºC. $[\alpha]_D^{22}$ 90.2 (c 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (d, *J* = 5.0 *Hz*, 3H), 3.76 – 3.85 (m, 4H), 4.01 (s, 3H), 5.02 (d, *J* = 7.4 *Hz*, 1H), 7.14 (d, *J* = 5.0 *Hz*, 1H), 7.56 (d, *J* = 5.0 *Hz*, 1H), 7.87 (s, 1H). HRMS (EI): calcd. for $C_{11}H_{24}N_2O_5S$: 286.0623, found: 286.0628.

(2*R*)-2-Amino-1-(4-methoxyphenyl)propane (1). (4*R*,5*S*)-5-(4-Methoxyphenyl)-4-methyloxazolidin -2-one (**8**, 1.8 g, 8.7 mmol) was dissolved in MeOH (30 mL). Into this solution was added Pd·C (0.4 g) and the resultant solution was stirred for 1h under atmospheric pressure of H_2 at rt. The solution was filtered and concentrated under in vacuo to afford the product[5] as an oil 1.43 g in 91% yield. Liquid. $[\alpha]_D^{22}$ −14.2 (c 2.3, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (d, *J* = 3.0 *Hz*, 3H), 2.14 (s, 2H), 2.61 – 2.64 (m, 2H), 3.26 – 3.29 (m, 1H), 3.92 (s, 3H), 6.96 – 6.72 (m, 2H), 7.21 – 7.28 (m, 2H).

(2*R*)-2-Amino-1-(4-methoxy-3-sulfamoylphenyl)propane (2). The same reaction as for the preparation of (1*R*)-5-(2-aminopropyl)-2-methoxybenzene (**1**, 1.4 g, 4.9 mmol) produced the target products from (4*R*,5*S*)-5-(4-methoxy-3-sulfamoylphenyl)-4-methyloxazolidine-2-on (**9**) in 87% yield. $[\alpha]_D^{22}$ –17.6 (c 1.0, MeOH) (lit.,[6]: $[\alpha]_D^{23}$ –17.3 (c 2.0, H_2O)). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.99 (d, *J* = 6.8 *Hz*, 3H), 2.54 (d, *J* = 7.2 *Hz*, 2H), 2.91 – 3.54 (m, 5H), 3.92 (s, 3H), 7.16 (d, *J* = 5.6 *Hz*, 1H), 7.41 (d, *J* = 5.8 *Hz*, 1H), 7.59 (s, 1H).

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