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# DIASTEREOSELECTIVE IODOAMIDATION OF 3-ACETOXYBUT-1-ENYLAMINES: SYNTHESIS OF 3-ACETOXY-4-IODO-2-(*p*-METHOXYBENZYL)PYRROLIDINES

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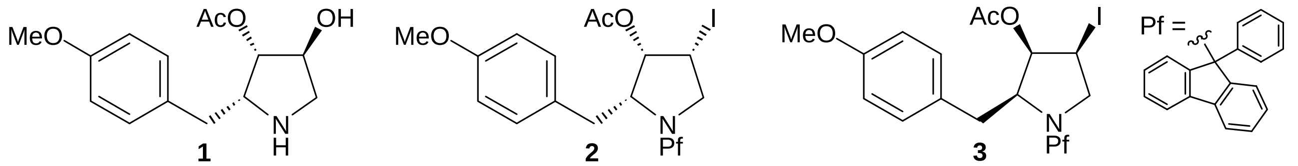
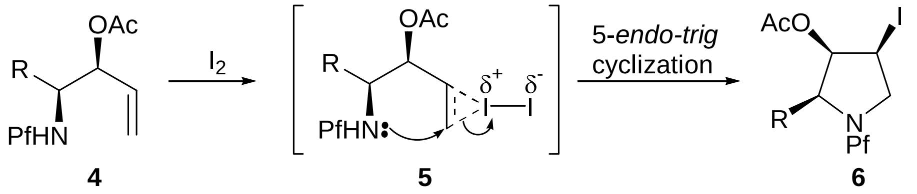
**Abstract**-3α-Acetoxy-4α-iodo-2α-(*p*-methoxybenzyl)pyrrolidine (**2**) and its enanti-omer (**3**) were synthesized *via* diastereoselective iodoamidation, starting from D- or L-tyrosine. The key step contains unfavorable 5-*endo*-*trig* cyclization and the diastereoselective addition of ethynylmagnesium bromide to aldehydes (**9**) by the chelation-controlled Cram cyclic model.

The antibiotic (-)-anisomycin (**1**) possessing a pyrrolidine skeleton, which was isolated from various *Streptomyces* species, exhibits selective action against protozoa and several strains of fungi.[1] It also has been shown to act as an inhibitor of protein synthesis,[1] and it finds wide use in the treatment of trichomonas vaginitis and amebic dysentery.[2] Because of its biological activity, many chemists have reported chiral synthesis of (-)-anisomycin (**1**) employing naturally occurring starting materials such as carbohydrates,[3] amino acids,[4] L-tartaric acis or its esters.[5] In this paper, we wish to report synthetic route for preparation of 3α-acetoxy-4α-iodo-2α-(*p*-methoxybenzyl)pyrrolidine (**2**) and its enantiomer (**3**) through unfavorable 5-*endo*-*trig* cyclization, starting from D- or L-tyrosine. We also found the diastereoselective addition of ethynylmagnesium bromide to aldehyde by the chelation-controlled Cram cyclic model (Scheme 1).



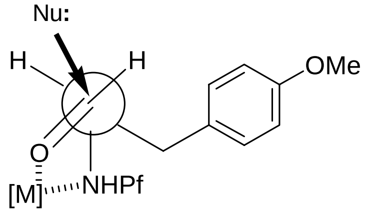
**Scheme 1**

Previously, we reported that 3-acetoxybut-1-enylamines (**4**) were easily transformed using iodine to pyrrolidine derivatives (**6**), precursors for aza sugars, *via* unfavorable 5-*endo-trig* cyclization of an intermediates (**5**) (Scheme 2).[6]



**Scheme 2**

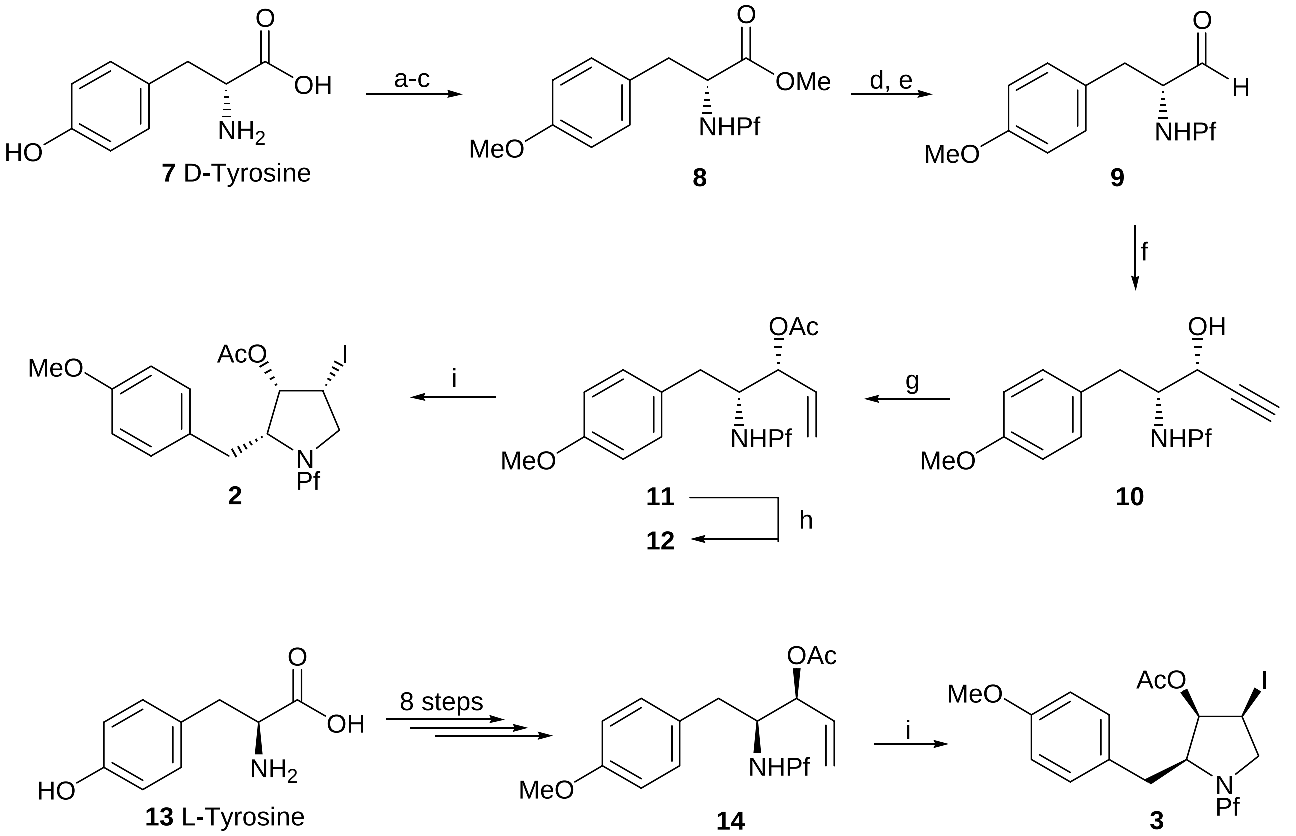
This tool should be allowed to apply for preparation of anisomycin derivatives. Compound (**8**) was synthesized easily by the usual method from commercially available D-tyrosine (**7**) in three high yielding steps. Then, we chose the 9-phenylfluoren-9-yl (Pf) group for protection of the amine since this protecting group has been shown to inhibit deprotonation at the α-position of α-amino ketones, esters, and aldehydes.[7] Ester (**8**) was reduced with $LiAlH_4$ in THF to give alcohol, which was subjected by Swern oxidation to give aldehyde (**9**). Treatment of aldehyde (**9**) with ethynmagnesium bromide in THF gave ethynyl alcohol (**10**) as a 10 : 1 mixture of *threo*- and *erythro*-isomers in 95% yield (*vide infra*), which could be isolated by column chromatography. Perhaps, the diastereoselectivity of the reaction of aldehyde (**9**) with ethynylmagnesium bromide is dependent on the presence of NHPf group. The *threo*-diastereoselectivity observed in the conversion of aldehyde (**9**) to **10** may be rationalized that the chelation-controlled Cram cyclic model[8] is more favorable than the Felkin-Anh transition state model as shown in Figure 1.[9] Thus, the attack by ethynylmagnesium bromide occurs from the less hindered side of the transition state (Figure 1) to give the *threo*-ethynyl alcohol (**10**) as the major product.



[M] = MgBr

**Figure 1** Transition State for *threo* Selectivity of Compound (**9**)

The ethynyl group of compound (**10**) was hydrogenated by treatment of compound (**10**) with Pd/$BaSO_4$ in the presence of quinoline to give the *threo*-allylic alcohol (**11**), which was protected with acetic anhydride to afford compound (**12**) in high yield. Compound (**12**) was treated with $I_2$ under biphasic conditions (saturated aq. $NaHCO_3$-THF-$Et_2O$ = 2 : 1 : 1) at room temperature for 3 h to give the all *cis*-pyrrolidine (**2**) with a 26 : 1 ratio of the *cis*- and *trans*-isomers in high yield *via* a diastereoselective iodoamidation. Pyrrolidine (**3**) $\{[\alpha]_D^{21}$ –22.9° (*c* 1.2, $CHCl_3$)$\}$ to be an enantiomer of **2** was also obtained with a 25 : 1 ratio of the *cis*- and *trans*-isomers form L-tyrosine using the standard condition (Scheme 3).



**Scheme 3** *Reagents and conditions*: (a) TMSCl/MeOH/r.t.. (b) PfBr/$Pb(NO_3)_2$/$Et_3N$/$CH_2Cl_2$/rt. (c) MeI/$K_2CO_3$/acetone/reflux. (d) $LiAlH_4$/THF/rt. (e) $(COCl)_2$/DMSO/$Et_3N$/$CH_2Cl_2$/-78 ºC-rt. (f) ethynylmagnesium bromide/THF/0 ºC. (g) Pd/$BaSO_4$/quinoline/MeOH/r.t.. (h) $Ac_2O$/$Et_3N$/DMAP (cat.)/$CH_2Cl_2$/rt. (i) $I_2$/saturated aq. $NaHCO_3$ : THF : $Et_2O$ = 2 : 1 : 1/rt.

Then, the stereochemistries of the products (**2**) and (**3**) were determined from their $^1$H-NMR analysis based on the coupling constant values and 2D-nOe experiments.[6]

In summary we have reported that 3α-acetoxy-4α-iodo-2α-(*p*-methoxybenzyl)pyrrolidines (**2**) and (**3**) were obtained by key steps of a diastereoselective iodoamidation of 3-acetoxybut-1-enylamines (**12**) and

(**14**) and the diastereoselective addition of ethynylmagnesium bromide to aldehydes by the chelation-controlled Cram cyclic model, using a strong electron-donating group, 9-phenylfluoren-9-yl, on amine moiety.

## EXPERIMENTAL

All non-aqueous reactions were carried out under nitrogen. THF was distilled from Na/benzophenone; $CH_2Cl_2$, $Et_3N$, and DMSO were distilled from $CaH_2$. Column chromatography was carried out using 230-400 mesh silica gel. Mps were measured on a Thomas-Hoover capillary apparatus and are uncorrected. $^1$H- and $^{13}$C-NMR spectra were measured down field relative to tetramethylsilane in $CDCl_3$ unless otherwise noted (values in ppm); coupling constants were reported in hertz; $^1$H-NMR, $^{13}$C-NMR and two-dimensional nuclear overhauser effect (2D nOe) experiments were conducted on a Bruker AW-500 spectrometer.

### 3-*p*-Methoxyphenyl-2α -*N*-9-phenylfluoren-9-ylamino-1-propanal (9)

D-Tyrosine (5.0 g, 27.60 mmol) was dissolved in TMSCl (10 mL) and MeOH (50 mL). After being stirred for 10 h at rt, the solution was evaporated, dried in vaccuo for 10 h, and the salt was dissolved in $CH_2Cl_2$ (90 mL). 9-Phenylfluoren-9-yl bromide (11.5 g, 35.88 mmol), lead nitrate (11.9 g, 35.88 mmol) and $Et_3N$ (7.7 mL, 55.2 mmol) were added. The mixture was stirred for 24 h at rt, and then it was filtered and chromatographed on silica gel (*n*-hexane : EtOAc = 20 : 1) to give *N*-protected methyl ester (10.86 g, 86%) as colorless needles. The *N*-protected methyl ester was dissolved in acetone (60 mL), and $K_2CO_3$ (4.9 g, 35.60 mmol) and iodomethane (7.4 mL, 118.7 mmol) were added. After refluxing for 36 h, the reaction was stopped by addition of 5% HCl. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude product was chromatographed on silica gel (*n*-hexane : EtOAc = 6 : 1) to give the compound (**8**) (10.5 g, 98%) as colorless prisms.

To an ice-cooled suspension of $LiAlH_4$ (1.3 g, 34.91mmol) in THF (116 mL) was added a solution of compound (**8**) (10.5 g, 23.27 mmol) in THF (100 mL). After being stirred for 10 min, the reaction mixture was quenched by addition of $H_2O$ (10 mL), 15% aq. NaOH (10 mL), and $Et_2O$ (100 mL), and then stirred for additional 20 min. The mixture was filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel (*n*-hexane : EtOAc = 4 : 1) to give alcohol compound (8.8 g, 90%) as colorless prisms. To oxalyl chloride (4.6 ml, 52.35 mmol) in $CH_2Cl_2$ (170 mL) at –78 ºC was added the solution of DMSO (5.9 ml, 83.8 mmol) in $CH_2Cl_2$ (50 mL) over 10 min and the mixture was stirred for 20 min. Alcohol (8.8 g, 20.94 mmol) in $CH_2Cl_2$ (80 mL) was added over 20 min and reacted for 20 min.

Finally, $Et_3N$ (23.3 ml, 167.5 mmol) was added over 15 min, and the solution was allowed to warm over 60 min, at which time the solution was poured into $Et_2O$ (200 mL) and 0.05 M phosphate buffer (pH 7.0) solution. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed successively with $H_2O$, 5% $NaHCO_3$ and brine, and dried over $MgSO_4$, concentrated, and chromatographed on silica gel (*n*-hexane : EtOAc = 10 : 1) to yield **9** (8.3 g, 95%) as colorless prisms, mp 38-40 ºC ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{20}$ +1.6 º(*c*1.0, $CHCl_3$); IR ($CHCl_3$) 3310, 3068, 2940, 1726, 1614 $cm^{-1}$; $^1H$-NMR (500 MHz, $CDCl_3$) δ 2.53-2.62 (m, 2H), 2.68 (m, 1H), 2.76 (br s, 1H), 3.78 (s, 3H), 6.68-7.65 (m, 17H), 9.23 (d, *J* = 2.5 Hz, 1H); $^{13}C$-NMR (125 MHz, $CDCl_3$) δ 34.8, 53.3, 61.1, 70.9, 112.1, 117.8, 118.1, 122.9, 123.7, 124.1, 125.3, 125.8, 126.0, 126.3, 126.4, 126.9, 128.5, 138.6, 138.7, 142.3, 146.7, 146.8, 156.7, 201.0. Anal. Calcd for $C_{29}H_{25}NO_2$: C, 83.02; H, 6.01; N, 3.34. Found: C, 82.75; H, 5.71; N, 3.61.

**4α -*N*-9-Phenylfluoren-9-ylamino-3α-hydroxy-5-*p*-methoxyphenyl-1-pentene (10)**

To a solution of **9** (8.3 g, 19.89 mmol) in THF (100 mL) was added ethynylmagnesium bromide (79.6 mL, 39.8 mmol) (0.5 M solution in THF) at 0 ºC. After being stirred for 30 min, the reaction mixture was quenched by addition of 5% HCl. The resulting mixture was extracted with EtOAc. The combined orgainc layers were with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting crude product was chromatographed on silica gel (*n*-hexane: EtOAc = 10 : 1) to give compound (**10**) (8.0 g, 90%) as colorless prisms, mp 63-65 ºC ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{22}$ +8.1 º (*c* 2.0, $CHCl_3$); IR (KBr) 3450, 3310, 3070, 1610 $cm^{-1}$; $^1H$-NMR (500 MHz, $CDCl_3$) δ 2.31 (br s, 1H), 2.37 (d, *J* = 2.1 Hz, 1H), 2.40 (dd, *J* = 6.8, 13.4 Hz, 1H), 2.52 (ddd, *J* = 4.3, 6.6, 6.6 Hz, 1H), 2.63 (dd, *J* = 6.4, 13.5 Hz, 1H), 3.76 (s, 3H), 3.85 (dd, *J* = 2.2, 4.2 Hz, 1H), 6.73-7.67 (m, 18H); $^{13}C$-NMR (125 MHz, $CDCl_3$) δ 36.5, 55.3, 58.7, 64.4, 72.5, 74.0, 83.4, 113.8, 119.8, 120.0,125.4, 125.8, 126.0, 127.2, 127.9, 128.2, 128.3, 128.5, 130.6, 140.2, 140.3, 145.4, 149.5, 149.6, 158.2. Anal. Calcd for $C_{31}H_{27}NO_2$: C, 83.56; H, 6.11; N, 3.15. Found: C, 83.81; H, 5.86; N, 2.95.

**4α-*N*-9-Phenylfluoren-9-ylamino-3α-hydroxy-5-*p*-methoxyphenyl-1-pentene (11)**

A solution of **10** (8.0 g, 17.9 mmol) in MeOH (45 mL) was hydrogenated under hydrogen atmosphere with Pd/$BaSO_4$ (10%, 0.8 mg) and quinoline (1.0 mL, 7.7 mmol) for 1 h. The mixture was filtered, the filtrate was evaporated, and the resulting crude product was chromatographed on silica gel (*n*-hexane: EtOAc = 10 : 1) to give compound (**11**) (7.6 g, 95%) as colorless prisms, mp 51-53 ºC ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{23}$ –115.3 º (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3450, 3070, 1610 $cm^{-1}$; $^1H$-NMR (500 MHz, $CDCl_3$) δ 2.22 (dd, *J* = 5.1, 13.3 Hz, 1H), 2.32 (m, 2H), 2.48 (dd, *J* = 8.3, 13.3 Hz, 1H), 3.69 (m, 1H), 3.72 (s, 3H), 5.01 (dt, *J* = 10.6, 1.6 Hz, 1H), 5.12 (dt, *J* = 17.3, 1.6 Hz, 1H), 5.52 (ddd, *J* = 4.9, 10.6, 17.3 Hz, 1H), 6.62-7.71 (m, 18H); $^{13}C$-NMR (125 MHz, $CDCl_3$) δ 36.9, 54.2, 57.8, 71.1, 71.7, 112.7, 114.1, 118.9, 124.5, 125.0, 125.4, 126.2, 126.7, 126.9, 127.3, 127.4, 127.5, 129.4, 130.0, 138.7, 139.3, 139.7, 144.3, 148.1, 149.1, 157.0. Anal. Calcd for $C_{31}H_{29}NO_2$: C, 83.18; H, 6.54; N, 3.13. Found: C, 83.25; H, 6.30; N, 3.34.

**4*α*-*N*-9-Phenylfluoren-9-ylamino-3*α*-acetoxy-5-*p*-methoxyphenyl-1-pentene (12)**

To a solution of **11** (7.6 g, 17.01 mmol) in $CH_2Cl_2$ (100 mL) was added $Et_3N$ (4.7 mL, 34.02 mmol) and acetic anhydride (3.2 ml, 34.02 mmol) in the presence of DMAP (cat.) at rt. After being stirred for 30 min, the reaction mixture was quenched by addition of 5% HCl and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The resulting residue was chromatographed on silica gel (*n*-hexane : EtOAc = 5 : 1) to give compound (**12**) (8.0 g, 99%) as colorless prisms, mp 51-52 ºC ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{23}$ –37.4 º (*c* 5, $CHCl_3$); IR (3327, 3063, 3017, 2934, 1737, 1611, 1511; $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.22 (m, 2H), 2.45 (m, 2H), 3.73 (s, 3H), 4.83 (m, 1H), 5.10 (dt, *J* = 16.0, 1.6 Hz, 1H), 5.20 (dt, *J* = 10.8, 1.6 Hz, 1H), 5.91 (ddd, *J* = 5.1, 10.8, 17.3 Hz, 1H), 6.58-7.71 (m, 17H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 20.9, 37.7, 55.2, 57.4, 72.7, 74.9, 113.7, 116.6, 119.7, 120.0, 125.3, 126.0, 126.2, 127.1, 127.7, 127.8, 128.1, 128.2, 128.4, 130.2, 131.0, 134.3, 140.2, 140.9, 145.6, 149.4, 149.9, 158.0, 169.5. Anal. Calcd for $C_{33}H_{31}NO_3$: C, 80.95; H, 6.38; N, 2.86. Found: C, 81.10; H, 6.62; N, 3.07.

***N*-9-Phenylfluoren-9-ylamino-3*α*-acetoxy-4*α*-iodo-2*α*-(*p*-methoxybenzyl)pyrrolidine (2)**

To a solution of **12** (8.0 g, 16.84 mmol) in biphasic solvent (saturated aq. $NaHCO_3$ : THF : $Et_2O$ = 2 : 1 : 1 ) was added $I_2$ (12.8 g, 50.52 mmol) at rt. After being stirred for 3 h, the reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ solution, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was chromatographed on silica gel (*n*-hexane : EtOAc = 10 : 1) to give *cis*-pyrrolidine (**2**) (9.5 g, 92%) as colorless prisms, mp 72-73 ºC ($CH_2Cl_2$/*n*-hexane); $[\alpha]_D^{20}$ +55.0 º (*c* 3, $CHCl_3$); IR (KBr) 3060, 3018, 2952, 1747, 1611, 1512 cm$^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.18 (dd, *J* = 3.3, 14.1 Hz, 1H), 2.65 (dd, *J* = 3.6, 9.3 Hz, 1H), 2.86 (dd, *J* = 11.0, 14.1 Hz, 1H), 3.17 (dd, *J* = 9.3, 11.1 Hz, 1H), 3.43 (ddd, *J* = 3.5, 7.1, 10.7 Hz, 1H), 3.55 (ddd, *J* = 3.6, 6.8, 10.9 Hz, 1H), 3.68 (s, 3H), 5.17 (t, *J* = 6.9 Hz, 1H), 6.57-7.75 (m, 17H); $^{13}$C-NMR (125 MHz, $CDCl_3$) δ 4.4, 21.4, 36.3, 55.6, 62.6, 63.1, 66.3, 76.2, 114.1, 120.5, 120.6, 127.0, 127.3, 127.6, 127.9, 128.4, 128.5, 128.6, 129.0, 129.3, 129.5, 129.7, 130.1, 130.6, 140.9, 141.3, 142.0, 146.2, 146.6, 158.2, 170.2. Anal. Calcd for $C_{33}H_{30}NO_3I$: C, 64.38; H, 4.92; N, 2.28. Found: C, 64.45; H, 5.12; N, 2.47.

## ACNOWLEDGEMENTS

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