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

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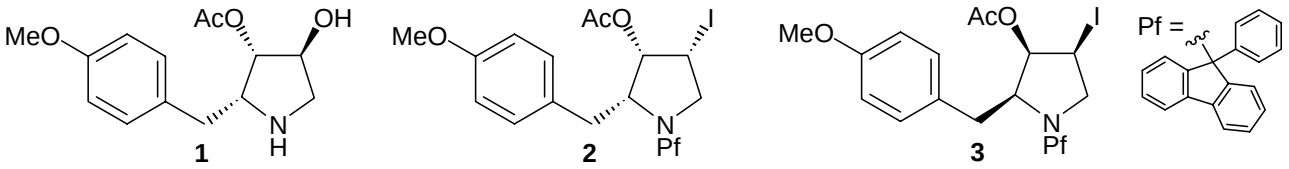
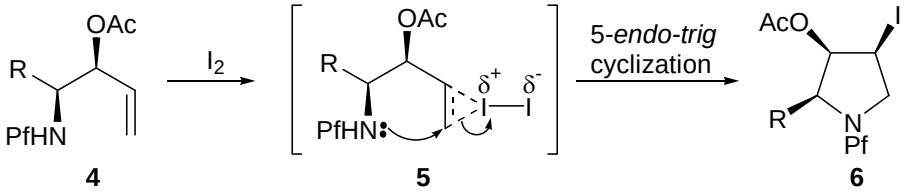
Abstract-3α-Acetoxy-4α-iodo-2α-(*p*-methoxybenzyl)pyrrolidine (**2**) and its enanti-omer (**3**) were synthesized *via* diastereoselective iodoamidation, starting from D- or L-tyrosine. The key step contains unfavorable 5-*endo-trig* cyclization and the diastereoselective addition of ethynylmagnesium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

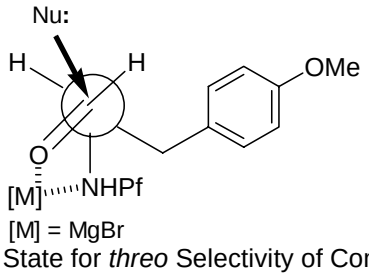
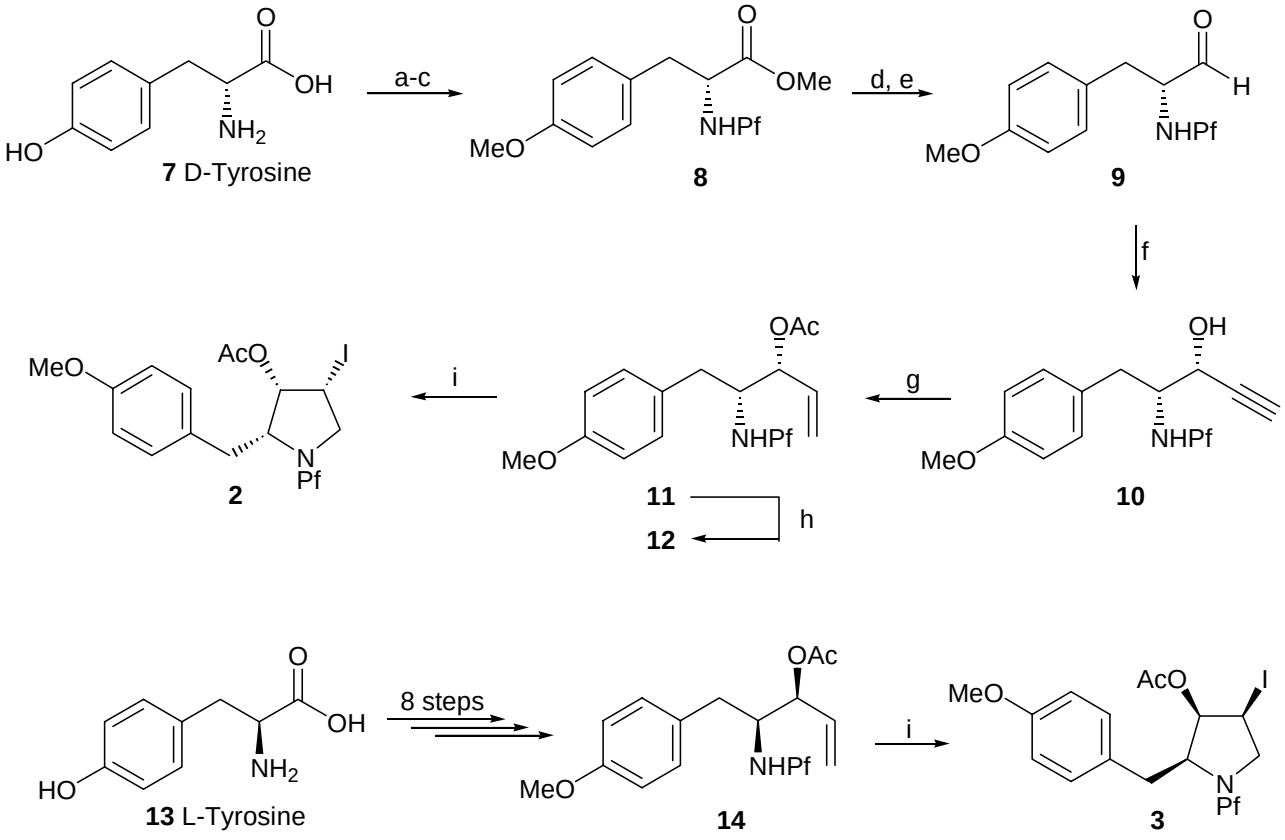


Figure 1 Transition State for *threo* Selectivity of Compound (**9**)

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}; ^{1}H-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.

4*α* -*N*-9-Phenylfluoren-9-ylamino-3*α*-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}; ^{1}H-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}; ^{1}H-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.

4α-*N*-9-Phenylfluoren-9-ylamino-3α-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-3α-acetoxy-4α-iodo-2α-(*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.

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